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(54) 3,6-ketal macrolide antibiotics

3,6-Ketal-Makrolidantibiotika

Antibiotiques macrolides de type 3,6-cétal

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WO-A-97/42204

- **ELLIOTT R L ET AL: "Novel 3-deoxy-3-descladinosyl-6-O-methyl erythromycin a analogues, synthesis and in vitro activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 7, no. 5, 4 March 1997, page 641-646 XP004136081**

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The file contains technical information submitted after the application was filed and not included in this specification

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Description

Background of the Invention

[0001] This invention relates to novel macrolide derivatives that may be useful in the treatment of bacterial, parasitic and protozoal infections in mammals, including man, as well as in fish and birds. This invention also relates to pharmaceutical compositions containing the novel compounds and to methods of treating bacterial, parasitic and protozoal infections in mammals, fish and birds by administering the novel compounds to mammals, fish and birds requiring such treatment.

[0002] Macrolide antibiotics are known to be useful in the treatment of a broad sprectrum of bacterial infections in mammals, including humans, fish and birds. Such antibiotics include various derivatives of erythromycin A such as azithromycin which is commercially available and is referred to in United States patents 4,474,768 and 4,517,359. Additional macrolides are referred to in United States provisional patent application serial number 60/049349, filed June 11, 1997 (Yong-Jin Wu); in United States provisional patent application serial number 60/046150, filed May 9, 1997 (Yong-Jin Wu); in United States provisional patent application serial number 60/063676, filed October 29, 1997 (Yong-Jin Wu); United States provisional patent application serial number 60/063161, filed October 29, 1997 (Yong-Jin Wu); United States provisional patent application serial number 60/054866, filed August 6, 1997 (Wei-Guo Su, Bingwei V. Yang, Robert G. Linde, Katherine E. Brighty, Hiroko Masamune, Yong-Jin Wu, Takushi Kaneko and Paul R. McGuirk); United States provisional patent application serial number 60/049348, filed June 11, 1997 (Brian S. Bronk, Michael A. Letavic, Takushi Kaneko, Bingwei V. Yang, Hengmiao Cheng, Edward Glazer) WO 98/01571 (International Application No. PCT/GB97/01810) filed July 4, 1997 (Peter Francis Leadlay, James Staunton, Jesus Cortes and Michael Stephen Pacey) WO 98/01546 (International Application No. PCT/GB97/01819), filed July 4, 1997 (Peter Francis Leadlay, James Staunton, and Jesus Cortes); United States provisional patent application entitled "Novel Macrolides", filed January 2, 1998 (John P. Dirlam); and United States provisional patent application entitled "Novel Erythromycin Derivatives", filed January 2, 1998 (Yong-Jin Wu). Like azithromycin and other macrolide antibiotics, the novel macrolide compounds of the present invention possess potent activity against various bacterial infections as described below.

[0003] Bio-organic and Medicinal Chemistry Letters 1997, 7(5), 641-646 discloses C-3 modified erythromycin A analogues with antibacterial activity. A number of oxime, carbonate and carbamate derivatives were synthesized and had reasonable activity against gram-positive bacteria.

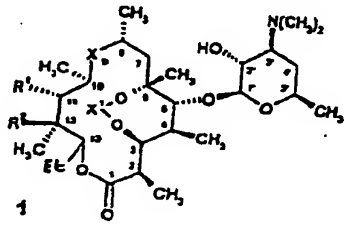
[0004] W097/42204 discloses 6-O substituted erythromycins and a method of making them. These compounds are also said to have antibacterial activity.

[0005] EPO682038 discloses 3-substituted derivatives of 5-O- desosaminylerythronolide which are said to have antibacterial activity.

[0006] EP0422843 discloses 6-O-methylerythromycin A oxime derivatives which are said to possess antibacterial activity.

Summary of the Invention

[0007] The present invention relates to compounds of formula 1



and to pharmaceutically acceptable salts or solvates thereof, wherein:

X is $-CH_2NR^6$- or $-NR^6CH_2$-, wherein the first dash of each of the foregoing X groups is attached to the C-10 carbon of the compound of formula 1 and the last dash of each group is attached to the C-8 carbon of the compounds of formula 1;

X' is

R^1 and R^2 are each OH;

R^3 is independently selected from the group consisting of H, C_1-C_6 alkyl, -$(CH_2)_m$(C_6-C_{10} aryl), and -$(CH_2)_m$(4-10 membered heterocyclic), wherein m is an integer ranging from 0 to 4 and the foregoing R^3 groups are optionally substituted by 1 to 3 R^{13} groups;

$R^{6'}$ is H, hydroxy, formyl, C_1-C_{10} alkoxy, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, -SO_2(C_1-C_{10} alkyl), -$(CH_2)_m$C(O)CH_2OC(O)(C_1-C_{10} alkyl), -$(CH_2)_m$C(O)$(CH_2)_t$$NR^{11}R^{12}$, -$(CH_2)_t$C(O)($C_1$-$C_{10}$ alkyl), -$(CH_2)_m$C(O)$(CH_2)_t$C(O)(C_1-C_{10} alkyl), -$(CH_2)_m$C(O)$(CH_2)_t$O(C_1-C_{10} alkyl), -$(CH_2)_m$C(O)$(CH_2)_t$O(C_2-C_{10} alkenyl), -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(4-10 membered heterocyclic), -C(O)$(CH_2)_m$C(O)$(CH_2)_q$(C_6-C_{10} aryl), -C(O)$(CH_2)_m$C(O)$(CH_2)_q$(4-10 membered heterocyclic), -$(CH_2)_m$C(O)$(CH_2)_q$(C_6-C_{10} aryl), -$(CH_2)_m$C(O)$(CH_2)_q$(4-10 membered heterocyclic), -$(CH_2)_q$C(O)$(CH_2)_m$O$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_q$C(O)$(CH_2)_m$O$(CH_2)_t$(4-10 membered heterocyclic), -$(CH_2)_t$O$(CH_2)_m$(C_6-C_{10} aryl), -$(CH_2)_t$O$(CH_2)_m$(4-10 membered heterocyclic), -$(CH_2)_m$P(O)R^3R^{16}, -$SO_2(CH_2)_t$(C_6-C_{10} aryl), or -$SO_2(CH_2)_t$(4-10 membered heterocyclic), -$(CH_2)_m$C(S)$(CH_2)_t$$NR^{11}R^{12}$, wherein m is an integer ranging from 0 to 4, q and t are each independently an integer ranging from 0 to 5, the heterocyclic moieties of the above $R^{6'}$ groups optionally include an oxo (=O) group on the ring system, and the foregoing $R^{6'}$ groups, except H, formyl and hydroxy, are optionally substituted by 1 to 3 R^{13} groups;

R^{11} and R^{12} are each independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, -C(O)(C_1-C_{10} alkyl), -$(CH_2)_m$(C_6-C_{10} aryl), -C(O)$(CH_2)_m$(C_6-C_{10} aryl), -$(CH_2)_m$(4-10 membered heterocyclic), and -C(O)$(CH_2)_m$(4-10 membered heterocyclic), wherein m is an integer ranging from 0 to 4, and the foregoing R^{11} and R^{12} groups, except H, are optionally substituted by 1 to 3 R^{13} groups;

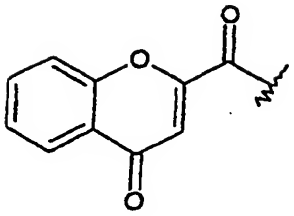
each R^{13} is independently selected from halo, cyano, nitro, trifluoromethyl, azido, -C(O)R^{16}, -C(O)OR^{16}, -OC(O)R^{16}, -OC(O)OR^{16}, -NR^{14}C(O)R^{15}, -C(O)$NR^{14}R^{15}$, -$NR^{14}R^{15}$, hydroxy, C_1-C_6 alkyl, -$N(SO_2R^{16})_2$, -$NR^{14}SO_2R^{16}$, -S(O)$_j$(C_1-C_6 alkyl) wherein j is an integer ranging from 0 to 2, C_1-C_6 alkoxy, -$(CH_2)_m$(C_6-C_{10} aryl), and -$(CH_2)_m$(4-10 membered heterocyclic), wherein m is an integer ranging from 0 to 4, and the alkyl, alkoxy, aryl and heterocyclic moieties of the above R^{13} subsituents are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, -C(O)R^{16}, -C(O)OR^{16}, -CO(O)R^{16}, -OC(O)OR^{16}, -NR^{14}C(O)R^{15}, -C(O)$NR^{14}R^{15}$, -$NR^{14}R^{15}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each R^{14} and R^{15} is independently H, -OR^7, C_1-C_6 alkyl, -$(CH_2)_m$(C_6-C_{10} aryl), or -$(CH_2)_m$(4-10 membered heterocyclic), wherein m is an integer ranging from 0 to 4, with the proviso that where R^{14} and R^{15} are both attached to the same nitrogen, then R^{14} and R^{15} are not both -OR^7; and

each R^{16} is independently selected from H, C_1-C_{10} alkyl, -$(CH_2)_m$(C_6-C_{10} aryl), and -$(CH_2)_m$(4-10 membered heterocyclic), wherein m is an integer ranging from 0 to 4.

[0008] More specific embodiments of this invention include compounds of formula 1 wherein

$R^{6'}$ is H, hydroxy, hydroxy substituted C_1-C_{10} alkyl, formyl, C_1-C_{10} alkoxy, -SO_2(C_1-C_4 alkyl), -$(CH_2)_m$C(O)(C_1-C_{10} alkyl), -$(CH_2)_m$C(O)CH_2OC(O)(C_1-C_{10} alkyl), -$(CH_2)_m$C(O)CH_2O(C_1-C_{10} alkyl), -$(CH_2)_m$C(O)$(CH_2)_q$(C_6-C_{10} aryl), -$(CH_2)_m$C(O)$(CH_2)_q$(4-10 membered heterocyclic), -$(CH_2)_t$(4-10 membered heterocyclic), or -$(CH_2)_t$(C_6-C_{10} aryl), where m, q and t are as defined above in the definition of $R^{6'}$. More preferred compounds include those wherein m, q and t are each independently 0 or 1. Other preferred compounds include those wherein $R^{6'}$ in the above piperidine group is selected from: -C(O)CH_2CH_3, -C(O)CH_2OCH_3, -C(O)H, -C(O)CH_2OH, -C(O)CH_2OC(O)CH_3, -C(O)CH_3, -4-chlorobenzyl, 2-pyridylmethyl, 4-acetamidobenzyl, 4-hydroxy-3-methoxybenzyl, 3-hydroxy-4-methoxybenzyl, 2-hydroxyethyl, -C(O)$CH_2N(CH_3)_2$, 4-quinolinylmethyl, 2-quinolinylmethyl, -C(O)CH_2OC(O)CH_3, -$SO_2CH_2CH_3$, -$SO_2CH(CH_3)_2$, 2-furoyl, benzoyl, 1-methyl-2-pyrrolylcarbonyl, 2-pyrazinylcarbonyl, 2-pyridylcarbonyl, 2-quinolinylcarbonyl, 3-pyridylcarbonyl, 3-cinnolinecarbonyl, 3-quinolinylcarbonyl, 4-benzyloxycarbonyl-2-fluorophenyl, and



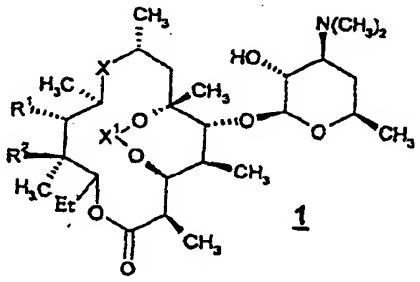
[0009] The invention also relates to a pharmaceutical composition for the treatment of a bacterial, parasitic or protozoal infection, or a disorder related to a bacterial, parasitic or protozoal infection, in a mammal, fish, or bird which comprises a therapeutically effective amount of a compound of formula 1 or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

[0010] The invention also relates to a method of treating a bacterial, parasitic or protozoal infection, or a disorder related to a bacterial, parasitic or protozoal infection, in a mammal, fish, or bird which comprises administering to said mammal, fish or bird a therapeutically effective amount of a compound of formula 1 or a pharmaceutically acceptable salt or solvate thereof.

[0011] The invention also relates to a pharmaceutical composition for the treatment of cancer, in particular non-small cell lung cancer, in a mammal, in particular a human, which comprises a therapeutically effective amount of a compound of formula 1 or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

[0012] The invention also relates to a method of treating cancer, in particular non-small cell lung cancer, in a mammal, which comprises administering to said mammal a therapeutically effective amount of a compound of formula 1 or a pharmaceutically acceptable salt or solvate thereof.

[0013] The invention also relates to a method of preparing a compound of the formula 1



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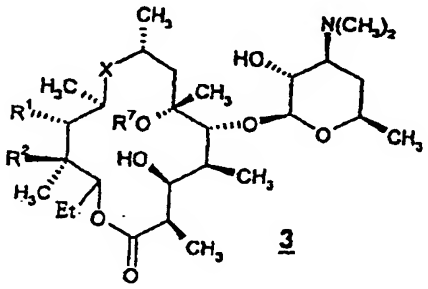
as defined above, which comprises treating a compound of the formula



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with a compound of formula:

in an aprotic solvent, preferably methylene chloride, in the presence of pyridinium p-toluenesulfonate and/or p-toluenesulfonic acid monohydrate.

[0014] The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

[0015] As used herein, unless otherwise indicated, the terms or phrases "bacterial, parasitic or protozoal infection", or "disorder related to a bacterial, parasitic or protozoal infection" include the following: pneumonia, otitis media, sinusitus, bronchitis, tonsillitis, and mastoiditis related to infection by *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus,* or *Peptostreptococcus* spp.; pharynigitis, rheumatic fever, and glomerulonephritis related to infection by *Streptococcus pyogenes*, Groups C and G streptococci, *Clostridium diptheriae*, or *Actinobacillus haemolyticum;* respiratory tract infections related to infection by *Mycoplasma pneumoniae, Legionella pneumophila, Streptococcus pneumoniae, Haemophilus influenzae,* or *Chlamydia pneumoniae;* uncomplicated skin and soft tissue infections, abscesses and osteomyelitis, and puerperal fever related to infection by *Staphylococcus aureus,* coagulase-positive staphylococci (i.e., *S. epidermidis, S. hemolyticus,* etc.), *Streptococcus pyogenes, Streptococcus agalactiae,* Streptococcal groups C-F (minute-colony streptococci), viridans streptococci, *Corynebacterium minutissimum, Clostridium* spp., or *Bartonella henselae;* uncomplicated acute urinary tract infections related to infection by *Staphylococcus saprophyticus* or *Enterococcus* spp.; urethritis and cervicitis; sexually transmitted diseases related to infection by *Chlamydia trachomatis, Haemophilus ducreyi, Treponema pallidum, Ureaplasma urealyticum,* or *Neisseria gonorrheae;* toxin diseases related to infection by *S. aureus* (food poisoning and toxic shock syndrome), or Groups A, B, and C streptococci; ulcers related to infection by *Helicobacter pylori;* systemic febrile syndromes related to infection by *Borrelia recurrentis;* Lyme disease related to infection by *Borrelia burgdorferi;* conjunctivitis, keratitis, and dacrocystitis related to infection by *Chlamydia trachomatis, Neisseria gonorrhoeae, S. aureus, S. pneumoniae, S. pyogenes, H. influenzae,* or *Listeria* spp.; disseminated *Mycobacterium avium* complex (MAC) disease related to infection by *Mycobacterium avium,* or *Mycobacterium intracellulare;* gastroenteritis related to infection by *Campylobacter jejuni;* intestinal protozoa related to infection by *Cryptosporidium* spp.; odontogenic infection related to infection by viridans streptococci; persistent cough related to infection by *Bordetella pertussis;* gas gangrene related to infection by *Clostridium perfringens* or *Bacteroides* spp.; and atherosclerosis or cardiovascular disease related to infection by *Helicobacter pylori* or *Chlamydia pneumoniae.* Bacterial infections and protozoal infections, and disorders related to such infections, which may be treated or prevented in animals include the following: bovine respiratory disease related to infection by *P. haemolytica, P. multocida, Mycoplasma bovis,* or *Bordetella* spp.; cow enteric disease related to infection by *E. coli* or protozoa (i.e., coccidia, cryptosporidia, etc.); dairy cow mastitis related to infection by Staph. aureus, *Strep. uberis, Strep. agalactiae, Strep. dysgalactiae, Klebsiella* spp., *Corynebacterium,* or *Enterococcus* spp.; swine respiratory disease related to infection by *A. pleuro., P. multocida,* or *Mycoplasma* spp.; swine enteric disease related to infection by *E. coli, Lawsonia intracellularis, Salmonella,* or *Serpulina hyodysinteriae;* cow footrot related to infection by *Fusobacterium* spp.; cow metritis related to infection by *E. coli;* cow hairy warts related to infection by *Fusobacterium necrophorum* or *Bacteroides nodosus*; cow pink-eye related to infection by *Moraxella bovis;* cow premature abortion related to infection by protozoa (i.e. neosporium); urinary tract infection in dogs and cats related to infection by *E. coli*; skin and soft tissue infections in dogs and cats related to infection by *Staph. epidermidis, Staph. intermedius, coagulase neg. Staph.* or *P. multocida;* and dental or mouth infections in dogs and cats related to infection by *Alcaligenes* spp., *Bacteroides* spp., *Clostridium* spp., *Enterobacter* spp., *Eubacterium, Peptostreptococcus, Porphyromonas,* or *Prevotella.* Other bacterial infections and protozoal infections, and disorders related to such infections, which may be treated or prevented in accord with the method of the present invention are referred to in J. P. Sanford et al., "The Sanford Guide To Antimicrobial Therapy," 26th Edition, (Antimicrobial Therapy, Inc., 1996).

[0016] The term "halo", as used herein, unless otherwise indicated, includes fluoro, chloro, bromo or iodo. Preferred halo groups are fluoro, chloro and bromo.

[0017] The term "alkyl", as used herein, unless otherwise indicated, means saturated monovalent hydrocarbon radicals having straight, cyclic or branched moieties.

[0018] The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl, as well as benzo-fused carbocyclic moieties such as 5,6,7,8-tetrahydro-naphthyl.

[0019] The term "4-10 membered heterocyclic", as used herein, unless otherwise indicated, includes aromatic and

non-aromatic heterocyclic groups containing one or more heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 4-10 atoms in its ring system. Non-aromatic heterocyclic groups include groups having only 4 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems and ring systems substituted with one or two oxo moieties. An example of a 5 membered heterocyclic group is thiazolyl, and an example of a 10 membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, piperidino, morpholino, thiomorpholino and piperazinyl. Non-aromatic heterocyclic groups include saturated and partially un-saturated ring systems. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl and thiazolyl. Heterocyclic groups having a fused benzene ring include chroman, benzodihydrofuran and benzimidazolyl. Heterocyclic groups having one or two oxo moieties include phthalimide and uracil.

[0020] The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of the present invention. The compounds of the present invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. The compounds of the present invention that include an amino moiety may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above.

[0021] Those compounds of the present invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline earth metal salts and, particularly, the calcium, magnesium, sodium and potassium salts of the compounds of the present invention.

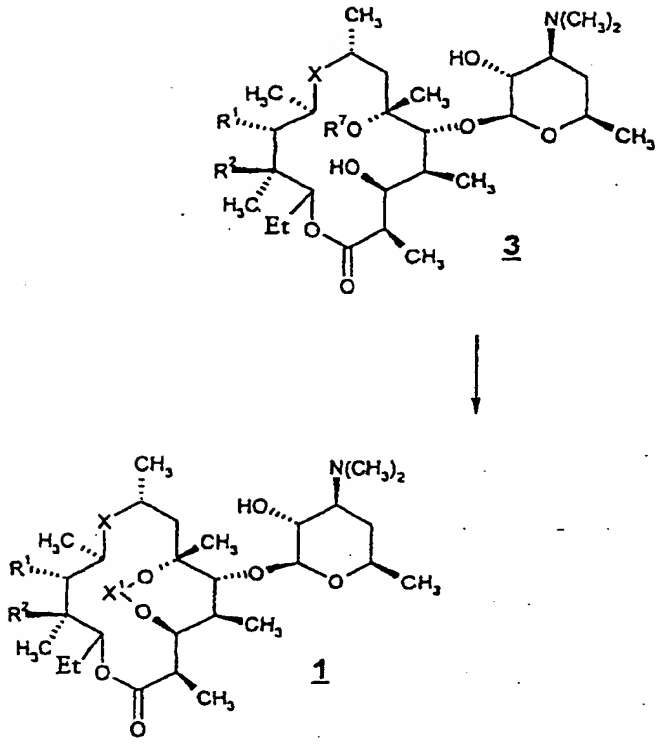
[0022] Certain compounds of the present invention may have asymmetric centers and therefore exist in different enantiomeric and diastereomeric forms. This invention relates to the use of all optical isomers and stereoisomers of the compounds of the present invention, and mixtures thereof, and to all pharmaceutical compositions and methods of treatment that may employ or contain them.

[0023] The present invention includes the compounds of the present invention, and the pharmaceutically acceptable salts thereof, wherein one or more hydrogen, carbon or other atoms are replaced by isotopes thereof. Such compounds may be useful as research and diagnostic tools in metabolism pharmacokinetic studies and in binding assays.

Detailed Description of the Invention

[0024] The preparation of the compounds of the present invention is illustrated in the following Scheme. In the following Scheme, unless otherwise indicated, X, R^1, R^2, and X^1 are as defined above.

Scheme 1



[0025] This invention uses a variety of macrolide templates as starting materials. They include azalides such as N9a-desmethyl azithromycin, azithromycin, erythromycin, clarithromycin, erythromycylamine as well as their analogs. Azithromycin can be prepared according to methods described in United States Patents 4,474,768 and 4,517,359, referred to above. Erythromycin can be prepared, or isolated, according to methods described in United States Patents 2,653,899 and 2,823,203. Clarithromycin can be prepared according to methods described in United States patent 4,331,803. The macrolide template corresponding to the compound of formula 1 or 2 wherein R^1 and R^2 are taken together, R^1 is -N(R^7)- and R^2 is O, and X is -C(O)- can be prepared according to methods described in Journal of Organic Chemistry 53, 2340 (1988). The above macrolide templates may be converted to the corresponding descladinose templates by treating the compounds with acetyl chloride in methanol at approximately ambient temperature. These starting materials may or may not require proper functional group protection before various modifications can take place, and deprotection after desired modifications are complete. The most commonly used protecting groups for amino moieties in the macrolide compounds of this invention are benzyloxycarbonyl (Cbz) and t-butyloxycarbonyl (Boc) groups. Hydroxyl groups are generally protected as acetates or Cbz carbonates.

[0026] To protect amino moieties, in particular the C-9 amino moiety of erythromycylamine, the macrolide is treated with *t*-butyl dicarbonate in anhydrous tetrahydrofuran (THF), or benzyloxycarbonyl N-hydroxysuccinimide ester (Cbz-OSu), to protect the C-9 amino group as its *t*-butyl or benzyl carbamate. The Boc group is normally removed either by acid treatment or by following a two step procedure as follows: (1) treatment with an excess amount (10 equivalents) of trimethylsilyl triflate in dichloromethane in the presence of 2,6-lutidine, and (2) desilylation with tetra-*n*-butylammonium fluoride in THF. The Cbz groups can be removed by conventional catalytic hydrogenation.

[0027] The C-2' hydroxyl group is a reactive hydroxyl group among the numerous hydroxyl groups present in macrolide compounds of the type claimed herein. The C-2' hydroxyl group is selectively protected by treating the compound with one equivalent of acetic anhydride in dichloromethane in the absence of external base. This process selectively converts the C-2' hydroxyl group into the corresponding acetate. The hydroxyl protecting group can be removed by treating the compound with methanol at a temperature ranging from about 0°C to about 65°C for 2 to 48 hours.

[0028] Alternatively, where the starting material for the preparation of the compounds of this invention is erythromycylamine or N9a-desmethyl azithromycin, these compounds can be treated with an excess of benzylchloroformate in THF/water at a pH of about 9 to provide N-9,2'-bis-Cbz protected erythromycylamine or N_{9a}-desmethyl azithromycin. In this process, the amino group and the C-2' hydroxyl group can be protected in one step.

[0029] With reference to the above Scheme 1, the compound of formula 3 may be converted to the compounds of formula 1 by treating the compound of formula 3 with a compound of the formula

in an aprotic solvent, preferably methylene chloride, in the presence of pyridinium p-toluenesulfonate and/or p-toluenesulfonic acid monohydrate at ambient temperature for a period of about 1 hour to 5 days. Specific preparations that have been employed to prepare the compounds of formula 1 are described below as Methods A-AP. In the following preparations, the following abbreviations may be used: Et (ethyl), Me (methyl), and HOBT (1-hydroxybenzotriazole hydrate), THF (tetrahydrofuran), DMF (N,N-dimethylformamide), and EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride).

Method A

Descladinose-azithromycin-3,6-cyclohexyl ketal; O-3; O-6 cyclohexylidenedescladinose-azithromycin; and Descladinose azithromycin-3-(1-cyclohexenyl) ether

[0030] To a solution of descladinose azithromycin (1.33 g, 2 mmol) in dry methylene chloride (100 ml) was added 1-methoxycyclohexene (13.44 g, 120 mmol) and pyridinium p-toluenesulfonate (3.0 g, 12 mmol). The solution was stirred under nitrogen at room temperature for four days. Dilute potassium carbonate solution was added, and the organic layer separated, washed with brine, dried over sodium sulfate, and filtered. The solvent was removed *in vacuo*, and the residue purified by flash chromatography (75 g silica, 0.8% concentrated ammonium hydroxide in 8% methanol/methylene chloride) to give descladinose-azithromycin-3,6-cyclohexyl ketal (400 mg, 0.59 mmol, 30%), mass spectrum 672. Descladinose azithromycin-3-(1-cyclohexenyl) ether was also isolated (120 mg, 0.18 mmol, 9% yield), mass spectrum 672.

Method B

N-Desmethyl-descladinose-azithromycin-3,6-(4-oxocyclohexyl) ketal and N-Desmethyl-descladinose azithromycin-3-(4-[5,6-dihydropyranyl]) ether

[0031] To a solution of, N-desmethyl-descladinose azithromycin (5.77 g, 10 mmol) in dry methylene chloride (200 ml) was added 5,6-dihydro-4-methoxy-pyran (22.8 g, 200 mmol), pyridinium p-toluenesulfonate (15.08 g, 60 mmol) and p-toluenesulfonic acid monohydrate (4.0 g, 21 mmol). The mixture was stirred at room temperature under nitrogen for 9.5 hours, washed with dilute potassium carbonate and brine, and filtered. The filtrates from four identical reactions were combined and concentrated under reduced pressure. The residue was divided into three equal portions and each was purified by flash chromatography (1 kg silica, 0.8% concentrated ammonium hydroxide in 8% methanol/methylene chloride). Impure fractions were re-chromatographed on 450 g silica with the same solvent, to give a total of 15.95 g (24.2 mmol, 60.5%) of N-desmethyl-descladinose-azithromycin-3,6-(4-oxocyclohexyl) ketal, mass spectrum 659.5. N-Desmethyl-descladinose azithromycin-3-(4-[5,6-dihydropyranyl]) ether was also isolated (1.97 g, 2.99 mmol, 7.5% yield), mass spectrum 659.5.

Method C

Descladinose azithromycin-3,6-(4-acetyl-4-azacyclohexyl) ketal

[0032] To a solution of descladinose azithromycin (950 mg, 1.62 mmol) in methylene chloride (90 ml) was added 1-acetyl-4-methoxy-1,2,3,6-tetrahydropyridine (7.55 g, 48.7 mmol) and p-toluenesulfonic acid monohydrate (941 mg, 4.95 mmol).. The mixture was stirred at room temperature under nitrogen for four days, diluted with methylene chloride, washed with dilute potassium carbonate and brine, dried over sodium sulfate, filtered, and concentrated under reduced

pressure. The residue was purified by successive silica gel flash chromatography (150 g silica with 0.3:2:8:10 concentrated ammonium hydroxide/methanol/acetone/benzene, 85 g silica with 25:1 acetonitrile/concentrated ammonium hydroxide, 35 g silica with 0.6 % concentrated ammonium hydroxide in 6% methanol/methylene chloride) to give the title compound (310 mg, 26.8% yield), mass spectrum 714.5.

Method D

Descladinose azithromycin-3,6-(4-carbobenzyloxy-4-azacyclohexyl) ketal

[0033] To a solution of of descladinose azithromycin (960 mg, 1.62 mmol) in methylene chloride (60 ml) was added 1-carbobenzyloxy-4-methoxy-1,2,3,6-tetrahydropyridine (12 g, 48.6 mmol), pyridinium p-toluenesulfonate (2.44 g, 9.72 mmol) and p-toluenesulfonic acid monohydrate (616 mg, 3.24 mmol). The mixture was stirred at room temperature two days, diluted with methylene chloride, washed with dilute potassium carbonate and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (100 g silica, 0.3/6/100 concentrated ammonium hydroxide/methanol/methylene chloride) to give the title compound (672 mg, 51.5% yield), mass spectrum 807.8.

Method E

Descladinose-azithromycin-3,6-(4-thiocyclohexyl) ketal

[0034] To a solution of of descladinose azithromycin (443 mg, 0.75 mmol) in dry methylene chloride (30 ml) was added 5,6-dihydro-4-methoxy-thiopyran (2.13 g of 72% mixture with the thioketone, est. 11.7 mmol), pyridinium p-toluenesulfonate (1.13 g, 4.5 mmol) and p-toluenesulfonic acid monohydrate (299 mg, 1.575 mmol). The mixture was stirred at room temperature under nitrogen for 24 hours, washed with dilute potassium carbonate and brine, and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (60 g silica, 0.6% concentrated ammonium hydroxide in 6% methanol/methylene chloride) to give the title compound (352 mg, 68% yield, mass spectrum 689.4).

Method F

N-Desmethyl-descladinose azithromycin-3,6-(4-acetyl-4-azacyclohexyl) ketal

[0035] To a solution of N-desmethyl-descladinose azithromycin 36.67g, 63.55 mmol) in methylene chloride (1400 ml) was added 1-acetyl-4-methoxy-1,2,3,6-tetrahydropyridine (197 g, 1.271 mol), pyridinium p-toluenesulfonate (95.82 g, 0.381 mol) and p-toluenesulfonic acid monohydrate (33.85g, 0.178 mol). The mixture was stirred at room temperature under nitrogen four days.

[0036] The mixture was diluted with methylene chloride (1.5 l, washed twice with dilute potassium carbonate (1 l and then brine (500 ml), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase prep HPLC with the following conditions. A 100 x 500 mm column packed with 15 µm Inertsil C-8 gel was equilibrated to a stable baseline with 100% (0.050M NH_4OAc + 0.1% NH_4OH; "buffer") at 400 ml per minute. The crude residue was converted to the citric acid salt in 200 ml of water. The clear solution was loaded onto the column using a sample loading pump. This column was eluted with 100% buffer for 2 minutes, followed by a gradient from 100% buffer to 20% buffer and 80% CH_3CN in 80 minutes. The detector was set at 230nm. Fractions collected were analyzed by reverse phase HPLC. Fractions >97% purity were combined and concentrated to remove CH_3CN. $NaHCO_3$ was added and the product extracted with 2 x 21 $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated to a white amorphous solid (27.5 g, 39.2 mmol, 61.7%), mass spectrum 700.3.

[0037] Alternatively, the product may be obtained with an extractive workup.

[0038] After the reaction was judged to be complete, the crude reaction mixture was transferred to a separatory funnel and was washed with an equal volume of 10% K_2CO_3. The aqueous phase was discarded, the organic phase was concentrated to low volume and was azeotroped several times with toluene to remove pyridine. The thick brown liquid was then suspended in water (for a typical 300 gram reaction done in 15 liters of CH_2Cl_2, 10 liters of water was used) and adjusted to pH 5.0 with H_3PO_4. The aqueous layer was washed with $CHCl_3$ (4x41). The pH was adjusted to pH 8.0 with $NaHCO_3$ and the product was extracted with 2 x 4 liters CH_3Cl_2. The combined organic layers were dried over $NaSO_4$, filtered and concentrated to a bright yellow solid. The recovery at this point was approximately equal to the weight of the descladinose azalide starting material.

[0039] The enol ether side product in the crude solid was hydrolysed as follows. 100 grams of solid was dissolved in 1600 ml of THF. To the solution was added 400 ml 1N HCL and the reaction was stirred while monitoring the reaction

for the disappearance of enol ether. After the reaction was complete (~120-180 minutes at room temperature) enough $NaHCO_3$ was added to neutralize the HCL. The solution was concentrated to remove THF and if needed enough $NaHCO_3$ was added until a pH of 8 was reached. The solution was extracted with 2x500 ml CH_2Cl_2. Organic layers were combined, dried over Na_2SO_4 and concentrated to a yellow foam, 73.7 grams.

[0040] For the final step, the solid was dissolved in 3 liters of 1:1 chloroform:dichloroethane and placed in a 6 liter Erlenmeyer flask. To the stirred solution was added 3 liters of 0.050M NH_4OAc + 0.1% TFA, and the mixture was stirred for 1 minute. The layers are separated, and the lower (organic) layer was dried over Na_2SO_4 and concentrated to a white foam (51.50 grams, >99% pure by HPLC).

Method G

Descladinose azithromycin-3,6-(4-azacyclohexyl) ketal

[0041] To a solution of descladinose azithromycin-3,6-(4-carbobenzyloxy-4-azacyclohexyl) ketal (460 mg, 0.57 mmol) in isopropanol (20 ml) in a Parr bottle was added 10% palladium on carbon (190 mg). The mixture was agitated under 52 psi hydrogen gas for two days, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20 g silica, 1/10/90 concentrated ammonium hydroxide/methanol/methylene chloride) to give the title compound (330 mg, 86.2% yield), mass spectrum 672.4.

Method H

Descladinose azithromycin-3,6-(4-methyl-4-azacyclohexyl) ketal

[0042] To a solution of descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (140 mg, 0.21 mmol) in acetonitrile (17 ml) was added a solution of sodium acetate trihydrate (286 mg, 2.1 mmol), acetic acid (126 mg, 0.12 ml, 2.1 mmol), and 37% aqueous formaldehyde (0.47 ml, 189 mg as formaldehyde, 6.3 mmol) in water (12 ml). The mixture was stirred one hour at room temperature, and sodium cyanoborohydride (39.6 mg, 0.63 mmol) was added. The mixture was stirred an additional two hours, most of the acetonitrile was removed under reduced pressure, and the residue was poured into dilute potassium carbonate, extracted into methylene chloride, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (5 g silica, 1% concentrated ammonium hydroxide in 10% methanol/methylene chloride) to give the title compound (93 mg, 64.6% yield), mass spectrum 686.5.

Method I

Descladinose azithromycin-3,6-(4-methanesulfonyl-4-azacyclohexyl) ketal

[0043] To a solution of descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (200 mg, 0.298 mmol) and triethylamine (60.3 mg, 0.083 ml, 0.596 mmol) in methylene chloride (2 ml) under nitrogen at -78°C was added methanesulfonyl chloride (37.5 mg, 0.025 ml, 0.328 mmol) dropwise over two minutes. The mixture was stirred five minutes at -78°C and allowed to warm to room temperature. After an additional hour of stirring, the mixture was diluted with methylene chloride, washed with dilute potassium carbonate and brine, dried over sodium sulfate, filtered, and evaporated. The residue was purified by flash chromatography (20g silica, 0.6% concentrated ammonium hydroxide in 6% methanol/methylene chloride) to give the title compound (135 mg, 60.4% yield), mass spectrum 750.5.

Method J

Descladinose azithromycin-3,6-(4-butanesulfonyl-4-azacyclohexyl) ketal

[0044] To a solution of descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (305 mg, 0.453 mmol) and triethylamine (115 mg, 0.158 ml, 1.13 mmol) in methylene chloride (10 ml) under nitrogen at room temperature was added butanesulfonyl chloride (85.2 mg, 0.070 ml, 0.544 mmol) dropwise over one minute. The mixture was stirred one hour, diluted with methylene chloride, washed with dilute potassium carbonate and brine, dried over sodium sulfate, filtered, and evaporated. The residue was purified by flash chromatography (40g silica, 0.5% concentrated ammonium hydroxide in 5% methanol/methylene chloride) to give the title compound (216.1 mg, 60.2% yield), mass spectrum 792.4.

Method K

Descladinose azithromycin-3,6-(4-ethanesulfonyl-4-azacyclohexyl) ketal

[0045] To a solution of descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (302 mg, 0.45 mmol) and diisopropylethylamine (145 mg, 0.196 ml, 1.125 mmol) in methylene chloride (10 ml) under nitrogen at -78°C was added ethanesulfonyl chloride (69.4 mg, 0.051 ml, 0.54 mmol) in two portions. The mixture was stirred ten minutes at -78°C and allowed to warm to room temperature. After an additional hour of stirring, the mixture was diluted with methylene chloride, washed with dilute potassium carbonate and brine, dried over sodium sulfate, filtered, and evaporated. The residue was purified by flash chromatography (40g silica, 0.5% concentrated ammonium hydroxide in 5% methanol/methylene chloride) to give the title compound (231 mg, 67% yield), mass spectrum 764.4.

Method L

N-Desmethyl-descladinose azithromycin-3,6-(4-cyclopropylcarbonyl-4-azacyclohexyl) ketal

[0046] To a solution of N-desmethyl descladinose azithromycin-3,6-(4-azacyclohexyl)ketal (295 mg, 0.449 mmol) in dry methylene chloride (10 ml) under nitrogen at room temperature was added cyclopropanecarboxylic acid (77.3 mg, 0.898 mmol), triethylamine (136 mg, 0.188 ml, 1.35 mmol), 1-hydroxybenzotriazole hydrate (66.8 mg, 0.494 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (94.7 mg, 0.494 mmol). More methylene chloride (20 ml) was added to bring the reaction mixture into solution. After stirring 2 hours, the mixture was washed with dilute potassium carbonate and brine, dried over sodium sulfate, filtered, and evaporated. The residue was purified on a chromatotron (2mm plate), eluting with 7:1:0.1 methylene chloride/methanol/concentrated ammonium hydroxide to give the title compound (270 mg, 82.8% yield, mass spectrum 726.5).

Method M

Descladinose azithromycin-3,6-(4-(2-chloroethoxycarbonyl)-4-azacyclohexyl) ketal

[0047] To a solution of descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (333.3 mg, 0.496 mmol) in methylene chloride (10 ml) under nitrogen at room temperature was added diisopropylethylamine (128 mg, 0.173 ml, 0.992 mmol) and 2-chloroethyl chloroformate (63.8 mg, 0.046 ml, 0.446 mmol). The mixture was stirred 16 hours at room temperature, dilute with methylene chloride, washed with dilute potassium carbonate and brine, dried over sodium sulfate, filtered, and evaporated. The residue was purified by flash chromatography (40 g silica, 0.5% ammonium hydroxide in 5% methanol/methylene chloride) to give the title compound (255 mg, 0.328 mmol, 73% yield), mass spectrum 778.3.

Method N

N-Desmethyl-descladinose azithromycin-3,6-(4-allyloxycarbonyl-4-azacyclohexyl) ketal

[0048] To a solution of N-desmethyl-descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (292 mg, 0.444 mmol) in methylene chloride (10 ml) under nitrogen at room temperature was added triethylamine (89.8 mg, 0.124 ml, 0.888 mmol) and allylchloroformate (53.5 mg, 0.047 ml, 0.444 mmol). The mixture was stirred 3 hours at room temperature, diluted with methylene chloride, washed with dilute potassium carbonate and brine, dried over sodium sulfate, filtered, and evaporated. The residue was purified by flash chromatography (40 g silica, 0.5% ammonium hydroxide in 5% methanol/methylene chloride) to give the title compound (234 mg, 0.316 mmol, 71% yield), mass spectrum 742.3.

Method O

Descladinose azithromycin-3,6-(4-methoxycarbonyl-4-azacyclohexyl) ketal

[0049] To a solution of descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (1.67 g, 2.48 mmol) and 4-dimethylaminopyridine (304 mg, 2.48 mmol) in methylene chloride (12.4 ml) at 0°C under nitrogen was added methyl chloroformate (93.5 mg, 0.08 ml, 0.99 mmol). The mixture was stirred one hour and quenched with saturated sodium bicarbonate. The organic phase was washed with sodium bicarbonate solution and brine, dried over sodium sulfate, filtered, and evaporated. The residue was purified by flash chromatography (100g silica, 10% methanol/methylene chloride gradient to 15% methanol/methylene chloride, impure fractions repurified on 9.7 g silica with 1.7% ammonium hydroxide in 16/7/75 acetone/2-propanol/cyclohexane) to give the title compound (383 mg, 0.525 mmol, 53% yield), mass spec-

trum 730.7.

Method P

N-Desmethyl descladinose azithromycin-3,6-(4-methoxycarbonyl-4-azacyclohexyl) ketal

[0050] To N-desmethyl-descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (300 mg, 0.456 mmol) in a reaction vial was added dry methylene chloride (3 ml) and potassium carbonate 600 mg, 4.35 mmol) which had been ground and dried in a microwave oven. Methyl chloroformate (51.7 mg, 0.042 ml, 0.547 mmol) was added via syringe, and the mixture stirred at room temperature 16 hours. The reaction mixture was washed twice with brine, dried over sodium sulfate, and purified on a chromatotron (2mm plate) using 10/1/0.1 methylene chloride/methanol/ammonium hydroxide, to give the title compound (204 mg, 0.284 mmol, 62% yield), mass spectrum 716.4.

Method Q

Descladinose azithromycin-3,6-(4-allylurea-4-azacyclohexyl)ketal

[0051] To descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (200 mg, 0.3 mmol) in anhydrous methylene chloride (2.5 ml) at room temperature under nitrogen was added allyl isocyanate (30 mg, 0.032 ml, 0.362 mmol). The mixture was stirred two hours, diluted with methylene chloride,washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered, and evaporated. The residue was purified by flash chromatography (10 g silica, 1% ammonium hydroxide in 5% methanol/methylene chloride) to give the title compound (113 mg, 0.149 mmol, 41% yield), mass spectrum 755.5.

Method R

Descladinose azithromycin-3,6-(4-acetoxyacetyl-4-azacyclohexyl) ketal

[0052] To descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (200 mg, 0.3 mmol) in methylene chloride (5 ml) at room temperature under nitrogen was added pyridine (19.6 mg, 0.020 ml, 0.25 mmol) and acetoxyacetyl chloride (50.8 mg, 0.04 ml, 0.372 mmol). The mixture was stirred one hour, diluted with methylene chloride, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered, and evaporated. The residue was stirred in methanol (2 ml) one hour and evaporated. The residue was purified by flash chromatography (10 g silica, 2% ammonium hydroxide in 10% methanol/methylene chloride) to give the title compound (96.8 mg, 0.125 mmol, 41.7% yield), mass spectrum 772.4.

Method S

Descladinose azithromycin-3,6-(4-cyclopropylcarbonyl-4-azacyclohexyl) ketal

[0053] To descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (200 mg, 0.3 mmol) in methylene chloride (2.5 ml) at room temperature under nitrogen was added pyridine (19.6 mg, 0.020 ml, 0.25 mmol) and cyclopropanecarbonyl chloride (12.7 mg, 0.011 ml, 0.121 mmol). The mixture was stirred one hour, and methanol (1.3 ml) was added. The reaction was stirred an additional three hours, evaporated, taken up in methylene chloride, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered, and evaporated. The residue was purified by flash chromatography (10 g silica, 1% ammonium hydroxide in 5% methanol/methylene chloride) to give the title compound (135.7 mg, 0.183 mmol, 61% yield), mass spectrum 740.5.

Method T

Descladinose azithromycin-3,6-(4-hydroxyacetyl-4-azacyclohexyl) ketal

[0054] To descladinose azithromycin-3,6-(4-acetoxyacetyl-4-azacyclohexyl) ketal (20 mg, 0.026 mmol) in methanol (1 ml) was added potassium carbonate (2 mg, 0.014 mmol). The mixture was stirred 16 hours at room temperature and evaporated to give the title compound as a mixture with residual potassium salts (13.8 mg total weight), mass spectrum 730.6.

Method U

Descladinose azithromycin-3,6-(4-cyclopropyl-4-azacyclohexyl) ketal

[0055] To descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (168 mg, 0.25 mmol) in methanol (5 ml) was added [1-ethoxycyclopropyl)oxy]trimethylsilane (218 mg, 0.25 ml, 1.25 mmol), sodium cyanoborohydride (63 mg, 1 mmol), acetic acid (150 mg, 0.143 ml, 2.5 mmol) and 3A molecular sieves (150 mg). The mixture was heated to reflux under nitrogen for ten hours, filtered, concentrated, and diluted with methylene chloride and saturated sodium bicarbonate. The organic layer was separated, and the aqueous layer extracted with methylene chloride. The combined organic layers were washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered, and evaporated. The residue was purified by flash chromatography (5g silica, 0.4% ammonium hydroxide in 5% methanol/methylene chloride, gradient to 0.4% ammonium hydroxide in 6% methanol/methylene chloride) to give the title compound (56 mg, 0.079 mmol, 31.5% yield), mass spectrum 712.4.

Method V

Descladinose azithromycin-3,6-benzaldehyde acetal

[0056] To descladinose azithromycin (3 g, 5.08 mmol) in benzene (125 ml) was added benzaldehyde dimethyl acetal (7.7 g, 7.6 ml, 50.76 mmol) and p-toluenesulfonic acid monohydrate (20 mg). The reaction mixture was heated to reflux under a Dean-Stark trap for 24 hours, and additional benzaldehyde dimethyl acetal was added (15.4 g, 15.2 ml, 0.101 mol). Refluxing was continued for two more days, the benzene was removed under reduced pressure, and most of the excess benzaldehyde dimethyl acetal distilled off under vacuum. The residual oil was purified by successive silica gel flash chromatography, eluting with 0.2% ammonium hydroxide in 1% methanol/chloroform, to give the two diastereomers of the title compound (707 mg and 408 mg, total 1.64 mmol, 32% yield, absolute configurations not assigned), mass spectrum 679.6.

Method W

Descladinose-9-dihydroerythromycin-3,6-(4-methyl-4-azacyclohexyl) ketal

[0057] To a suspension of descladinose-9-dihydroerythromycin-3,6-(4-azacyclohexyl) ketal (250 mg, 0.379 mmol) in water (5 ml) was added formaldehyde (37% solution in water, 0.12 ml, 47.9 mg as formaldehyde, 1.6 mmol) and formic acid (0.57 ml, 695 mg, 15.1 mmol). The solution was heated to reflux for five hours, and stirred at room temperature for an additional 20 hours. The mixture was poured into saturated sodium bicarbonate solution and extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and evaporated to give the title compound (120 mg, 0.188 mmol, 50% yield), mass spectrum 637.4.

Method AB

Addition of Arylalkyl Groups to 3,6-Azacycloalkyl Ketals

[0058] To *N*-desmethyl-descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (250 mg to 500 mg) or descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (250 mg to 500 mg) in CH_2Cl_2 was added substituted benzyl bromide or substituted benzyl chloride (1.2 to 2 eq) and Et_3N (3 eq) at room temperature. The reaction mixture was stirred for 24-48 hours and quenched with saturated sodium bicarbonate solution. The organic layer was washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate, filtered and organic solvent removed *in vacuo*. The residue was purified by flash chromatography using 3-6% MeOH/$CHCl_3$, 0.5% ammonia to give the corresponding compound in which the nitrogen of the 4-azacyclohexyl moiety was substituted with the substituted benzyl group. When *N*-desmethyl-descladinose azithromycin-3,6-(4-azacyclohexyl) ketal was used, the disubstituted benzyl derivative (ring N-9a was also benzylated) was also isolated as a minor product.

Method AC

Procedure For Reductive Amination 3,6-Azacycloalkyl Ketals

[0059] To *N*-desmethyl-descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (250 mg to 500 mg) or descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (250 mg to 500 mg) in CH_2Cl_2, an aldehyde of the formula RC(O)H wherein

R corresponds to the various carbonyl moieties provided in the definition of R^6' referred to above, and specifically referred to in the tables of examples below (2.5 eq.), and sodium sulfate (10 eq.) or molecular sieves (3Å) were mixed in a round bottom flask and dried under vacuum. CH_2Cl_2 (10-20 ml) was added to the flask, followed by the addition of acetic acid (3 eq.), and the mixture was stirred at room temperature for 15 minutes. NaB(OAc)3H (2 eq.) was then added, and the stirring was continued at room temperature for 2 to 14 hours. The reaction was then quenched with saturated sodium bicarbonate solution, and the product was extracted with CH_2Cl_2 (3 x 50 ml. The combined organic layers were washed with brine, and dried with sodium sulfate, and organic solvent was removed *in vacuo* to give the crude product which was purified by flash chromatography using 3-5% MeOH/$CHCl_3$ and 0.5% concentrated ammonia.

Method AD

Procedure For Coupling Ketals With Aromatic Acids

[0060] *N*-desmethyl-descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (250 mg to 500 mg) or descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (250 mg to 500 mg), an acid of the formula RC(O)OH wherein R is defined as provided in Method AC (2 eq.), EDC (1.2 eq.), HOBT (1.2 eq.) were mixed and dried under vacuum. After the mixture was dissolved in CH_2Cl_2 (10 ml), Et_3N (4 eq.) was added, and the resulting solution was stirred at room temperature for 24 to 48 hours. The reaction was then quenched with saturated sodium bicarbonate solution, and the product was extracted with CH_2Cl_2 (3 x 50 ml). The combined organic layers were washed with brine, and dried with sodium sulfate, and organic solvent was removed *in vacuo* to give the crude product which was purified by flash chromatography using 3-5% MeOH/$CHCl_3$ and 0.5% concentrated ammonia.

Method AE

Descladinose azithromycin-3,6-(4-(1-propen-3-yl)-4-azacyclohexyl)ketal

[0061] Descladinose azithromycin-3,6-(4-azacyclohexyl)ketal (250 mg, 0.372 mmol) was dissolved in toluene (5ml), followed by the addition of Et_3N (259 µl, 1.86 mmol), $Pd(PPh_3)_4$ (43.0 mg, 0.0372 mmol), allyl acetate (48.0 µl, 0.446 mmol). The reaction mixture was stirred at 80 °C overnight, and TLC showed the reaction was complete. The reaction solution was taken into EtOAc, washed with saturated $NaHCO_3$ solution, water, and brine. The solvent was then removed *in vacuo* to give the crude product which was purified by flash chromatography using 6% methanol, 0.2% ammonia in chloroform to give the desired product (215 mg, 81% yield).

Method AF

N-desmethyl-descladinose azithromycin-3,6-(4-(5-nitropyridin-2-yl)-4-azacyclohexyl)ketal

[0062] A mixture of N-desmethyl-decladinose azithromycin-3,6-(4-azacyclohexyl)ketal (200mg, 0.30 mmol) and 2-chloro-5-nitro pyridine (73 mg, 1.5 equiv) in dry acetonitrile (1.4 ml) was treated with triethylamine (46 mg, 1.5 equiv) and the resulting mixture was refluxed 2 hours until completion of the reaction. The solvent was removed in vacuo and the crude mixture was purified by flash chromatography with 0-5% Et_2NH/EtOAc to provide the desired product (214.6 mg, 90%) as a pale yellow solid.

Method AG

N-desmethyl-descladinose azithromycin-3,6-(4-diphenylphosphinyl-4-azacyclohexyl)ketal

[0063] Descladinose azithromycin-3,6-(4-azacyclohexyl)ketal was dissolved in methylene chloride, and the resulting solution was stirred in an ice-water bath. Phosphinic chloride was added dropwise to the reaction flask, and the reaction was followed by TLC. After the reaction was finished, the reaction mixture was diluted with CH_2Cl_2, the organic layer was washed with saturated sodium bicarbonate solution, water, and brine. The organic layer was dried with sodium sulfate, and the solvent was removed *in vacuo* to give the crude product which was purified by flash chromatography.

Method AH

N-desmethyl-descladinose azithromycin-3,6- 4-(2-fluoro-4-benzyloxycarbonyl-phenyl)-4-azacyclohexyl)ketal

[0064] N-desmethyl-decladinose azithromycin-3,6-(4-azacyclohexyl)ketal (329 mg, 0.500 mmol) and benzyl 3,4-di-

fluorobenzoate were dissolved in isopropanol (2ml), followed by the addition of N,N-diisopropylethylamine (193 mg, 1.50 mmol). The reaction mixture was then heated at 85°C and followed by TLC. After 12 hours stirring, the reaction mixture was taken into methylene chloride (100mL), and washed with brine (100ml). The organic layer was dried with sodium sulfate, and the solvent was removed *in vacuo* to give the crude product which was purified by preparative TLC plate using 10% MeOH, 1% ammonia in methylene chloride to give the title compound (26 mg, 6% yield).

Method AI

N-desmethyl-descladinose azithromycin-3,6-(4-(2-fluoro-4-(4-pyridylmethylaminocarbonyl)-phenyl)-4-azacyclohexyl) ketal

[0065] N-desmethyl-descladinose azithromycin-3,6-(4-azacyclohexyl)ketal (300. mg, 0.446 mmol) and 4'-pyridylmethyl-3,4-difluorobenzoate were dissolved in DMF (2 ml), followed by the addition of N,N-diisopropylethylamine (173 mg, 1.34 mmol). The reaction mixture was then heated at 95°C and followed by TLC. After 48 hours stirring, the reaction mixture was taken into methylene chloride (100ml), and washed with brine (100 ml). The organic layer was dried with sodium sulfate, and the solvent was removed *in vacuo* to give the crude product which was purified by preparative TLC plate using 10% MeOH, 0.5% ammonia in methylene chloride to give the title compound (8 mg, 2% yield).

Method AK

N-desmethyl-N-benzyl-descladinose azithromycin-3,6-(4-(2-pyrazinylcarbonyl)-4-azacyclohexyl)ketal

[0066] N-desmethyl-descladinose azithromycin-3,6-(4-2'-pyrazinylcarbony-azacyclohexyl)-ketal (100 mg, 0.131 mmol) and benzyl bromide (31.0 µl 0.262 mmol) were dissolved in dioxane (1 ml), followed by the addition of Et_3N (55 µl, 0.393 mmol). After the reaction solution was stirred at room temperature for 12 hours, it was taken into CH_2Cl_2, and the organic layer was washed with saturated sodium bicarbonate solution. The organic layer was dried (Na_2SO_4), and solvent was removed in vacuo to give the crude product which was purified by flash chromatography using 6% MeOH, 0.5% ammonia in methylene chloride to give the title compound (8 mg, 7% yield).

Method AL

N-desmethyl-N-p-methoxybenzyl-descladinose azithromycin-3,6-(4-(pyrazinylcarbonyl)-4-azacyclohexyl)ketal

[0067] N-desmethyl-descladinose azithromycin-3,6-(4-2'-pyrazinylcarbonyl-4-azacyclohexyl) ketal (100 mg, 0.131 mmol) and p-methoxy-benzyl chloride (36.0 µl, 0.262 mmol) were dissolved in dioxane (1ml), followed by the addition of Et_3N (55 µl, 0.393 mmol). After the reaction solution was stirred at room temperature for 12 hours, it was taken into CH_2Cl_2, and the organic layer was washed with saturated sodium bicarbonate solution. The organic layer was dried (Na_2SO_4), and solvent was removed *in vacuo* to give the crude product which was purified by flash chromatography using 6% MeOH, 0.5% ammonia in methylene chloride to give the title compound (37.0 mg, 32% yield).

Method AM

N-desmethyl-descladinose azithromycin-3,6-(4-(2-benzyloxime)-propanoyl-4-azacyclohexyl)ketal

[0068] N-desmethyl-descladinose azithromycin-3,6-(4-pyruvyl-4-azacyclohexyl)ketal (150 mg, 0.206 mmol) and O-benzylhydroxylamine hydrochloride (165 mg, 1.03 mmol) were mixed in a vial equipped with a septum cap, followed by the addition of pyridine (1 ml). The vial was placed on a shaker, and the shaker was shaken at 60°C overnight. The reaction mixture was taken into methylene chloride, and washed with saturated $NaHCO_3$ solution, then brine. The organic layer was dried, and the solvent was removed *in vacuo* to give the title product in quantitative yield.

Method AN

N-desmethyl-descladinose azithromycin-3,6-(4-(2-pentafluorobenzyloxime)propanoyl-4-azacyclohexyl)ketal

[0069] N-desmethyl-descladinose azithromycin-3,6-(4-pyruvyl-4-azacyclohexyl)ketal (150 mg, 0.206 mmol) and O-pentafluorobenzylhydroxylamine hydrochloride (165 mg, 1.03 mmol) were mixed in a vial equipped with a septum cap, followed by the addition of pyridine (1ml). The vial was placed on a shaker, and the shaker was shaken at 60°C overnight. The reaction mixture was taken into methylene chloride, and washed with saturated $NaHCO_3$ solution, then

brine. The organic layer was dried, and the solvent was removed *in vacuo* to give the product in quantitative yield.

Method AO

N-desmethyl-descladinose azithromycin-3,6-(4-(2,2-di-(ethoxycarbonyl)-ethen-1-yl)4-azacyclohexyl)ketal

[0070] A solution of N-desmethyl-descladinose azithromycin-3,6-(4-azacyclohexyl)ketal (250 mg, 0.38 mmol) in dichloromethane under nitrogen was treated with the enone diethyl ethoxymethylene malonate (0.12 ml, 0.57 mmol) in one portion. The mixture was stirred at room temperature overnight, until the reaction was completed. The solvent was evaporated *in vacuo* and the resulting crude mixture was purified by flash column chromatography (45 g silica, 95:5:1 methylene chloride/methanol/ammonium hydroxide) to provide the desired product CP-547089 (37.9 mg) as a pale yellow solid.

Method AP

N-desmethyl-descladinose azithromycin-3,6-(4-(4-carbobenzyloxy-3-trifluoromethyl) phenyl-4-azacyclohexyl)ketal

[0071] To a solution of N-desmethyl-descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (1.47g, 2.23 mmol) and potassium carbonate (308 mg, 2.23 mmol) in acetonitrile (22 ml) was added benzyl 4-fluoro-2-(trifiouromethyl)benzoate (2.00 g, 6.71 mmol). The flask was fitted with a reflux condenser and heated to 82 °C for 7 days. After cooling to room temperature the solution was diluted with methylene chloride and filtered through celite. The filtrate was concentrated and the residue was purified by flash chromatography (silica gel, 0.2% ammonium hydroxide (10% aqueous) in 10% methanol/methylene chloride to give the title compound (470 mg, 23% yield), mass spectrum 937 (M + 1).

Method AQ

Descladinose azithromycin-3,6-(4-(thiazo-2-yl)-4-azacyclohexyl)ketal

[0072] To a solution of descladinose azithromycin-3,6-(4-azacyclohexyl) ketal (100 mg, 0.15 mmol) and diisopropylethylamine (0.036 ml. 0.21 mmol) in 2-propanol (1.5 mL) was added 2-chlorothiazole (0.014 ml 0.16 mmol). The flask was fitted with a reflux condenser and heated to 80°C for 24 hours. After cooling to room temperature the mixture was transferred to a separatory funnel and diluted with methylene chloride (20 ml). The mixture was washed with water (10 ml). The layers were separated and the aqueous fraction was extracted with methylene chloride (2 x 5 ml). The combined methylene chloride fractions were dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 0.2% ammonium hydroxide (10% aqueous) in 10% methanol/methylene chloride to give the title compound (54.6 mg, 48% yield), mass spectrum 756 (M + 1).

[0073] The compounds of the present invention may have asymmetric carbon atoms. Such diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art for example, by chromatography or fractional crystallization. All such isomers, including diastereomer mixtures, are considered as part of the invention.

[0074] The compounds of the present invention that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The desired acid salt can also be precipitated from a solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid.

[0075] Those compounds of the present invention that are acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of the present invention. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to

dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

[0076] The activity of the compounds of the present invention in the treatment of a bacterial, parasitic or protozoal infection, or a disorder related to a bacterial, parasitic or protozoal infection, may be assessed by subjecting the claimed compounds to one or more of the following assays.

Assay I

[0077] Assay I, described below, employs conventional methodology and interpretation criteria and is designed to provide direction for chemical modifications that may lead to compounds that circumvent defined mechanisms of macrolide resistance. In Assay I, a panel of bacterial strains is assembled to include a variety of target pathogenic species, including representatives of macrolide resistance mechanisms that have been characterized. Use of this panel enables the chemical structure/activity relationship to be determined with respect to potency, spectrum of activity, and structural elements or modifications that may be necessary to obviate resistance mechanisms. Bacterial pathogens that comprise the screening panel are shown in the table below. In many cases, both the macrolide-susceptible parent strain and the macrolide-resistant strain derived from it are available to provide a more accurate assessment of the compound's ability to circumvent the resistance mechanism. Strains that contain the gene with the designation of *ermA/ermB/ermC* are resistant to macrolides, lincosamides, and streptogramin B antibiotics due to modifications (methylation) of 23S rRNA molecules by an Erm methylase, thereby generally prevent the binding of all three structural classes. Two types of macrolide efflux have been described; *msrA* encodes a component of an efflux system in staphylococci that prevents the entry of macrolides and streptogramins while *mefA/E* encodes a transmembrane protein that appears to efflux only macrolides. Inactivation of macrolide antibiotics can occur and can be mediated by either a phosphorylation of the 2'-hydroxyl *(mph)* or by cleavage of the macrocyclic lactone (esterase). The strains may be characterized using conventional polymerase chain reaction (PCR) technology and/or by sequencing the resistance determinant. The use of PCR technology in this application is described in J. Sutcliffe et al., "Detection Of Erythromycin-Resistant Determinants By PCR", Antimicrobial Agents and Chemotherapy, 40(11), 2562-2566 (1996). The assay is performed in microtiter trays and interpreted according to Performance Standards for Antimicrobial Disk Susceptibility Tests - Sixth Edition; Approved Standard, published by The National Committee for Clinical Laboratory Standards (NCCLS) guidelines; the minimum inhibitory concentration (MIC) is used to compare strains. Compounds are initially dissolved in dimethylsulfoxide (DMSO) as stock solutions.

Strain Designation	Macrolide Resistance Mechanism(s)
Staphylococcus aureus 1116	susceptible parent
Staphylococcus aureus 1117	*ermB*
Staphylococcus aureus 0052	susceptible parent
Staphylococcus aureus 1120	*ermC*
Staphylococcus aureus 1032	*msrA, mph*, esterase
Staphylococcus hemolyticus 1006	*msrA, mph*
Streptococcus pyogenes 0203	susceptible parent
Streptococcus pyogenes 1079	*ermB*
Streptococcus pyogenes 1062	susceptible parent
Streptococcus pyogenes 1061	*ermB*
Streptococcus pyogenes 1064	*ermB*
Streptococcus agalactiae 1024	susceptible parent
Streptococcus agalactiae 1023	*ermB*
Streptococcus pneumoniae 1016	susceptible
Streptococcus pneumoniae 1046	*ermB*
Streptococcus pneumoniae 1095	*ermB*

(continued)

Strain Designation	Macrolide Resistance Mechanism(s)
Streptococcus pneumoniae 1175	*mefE*
Streptococcus pneumoniae 0085	susceptible
Haemophilus influenzae 0131	susceptible
Moraxella catarrhalis 0040	susceptible
Moraxella catarrhalis 1055	erythromycin intermediate resistance
Escherichia coli 0266	susceptible

[0078] Assay II is utilized to test for activity against *Pasteurella multocida* and Assay III is utilized to test for activity against *Pasteurella haemolytica.*

Assay II

[0079] This assay is based on the liquid dilution method in microliter format. A single colony of *P. multocida* (strain 59A067) is inoculated into 5 ml of brain heart infusion (BHI) broth. The test compounds are prepared by solubilizing 1 mg of the compound in 125 µl of dimethylsulfoxide (DMSO). Dilutions of the test compound are prepared using uninoculated BHI broth. The concentrations of the test compound used range from 200 µg/ml to 0.098 µg/ml by two-fold serial dilutions. The *P. multocida* inoculated BHI is diluted with uninoculated BHI broth to make a 10^4 cell suspension per 200 µl. The BHI cell suspensions are mixed with respective serial dilutions of the test compound, and incubated at 37°C for 18 hours. The minimum inhibitory concentration (MIC) is equal to the concentration of the compound exhibiting 100% inhibition of growth of *P. multocida* as determined by comparison with an uninoculated control.

Assay III

[0080] This assay is based on the agar dilution method using a Steers Replicator. Two to five colonies isolated from an agar plate are inoculated into BHI broth and incubated overnight at 37°C with shaking (200 rpm). The next morning, 300 µl of the fully grown *P. haemolytica* preculture is inoculated into 3 ml of fresh BHI broth and is incubated at 37°C with shaking (200 rpm). The appropriate amounts of the test compounds are dissolved in ethanol and a series of two-fold serial dilutions are prepared. Two ml of the respective serial dilution is mixed with 18 ml of molten BHI agar and solidified. When the inoculated *P. haemolytica* culture reaches 0.5 McFarland standard density, about 5 µl of the *P. haemolytica* culture is inoculated onto BHI agar plates containing the various concentrations of the test compound using a Steers Replicator and incubated for 18 hours at 37°C. Initial concentrations of the test compound range from 100-200 µg/ml. The MIC is equal to the concentration of the test compound exhibiting 100% inhibition of growth of *P. haemolytica* as determined by comparison with an uninoculated control.

[0081] The in vivo activity of the compounds of the present invention can be determined by conventional animal protection studies well known to those skilled in the art, usually carried out in rodents.

Assay IV

Murine *P. Multocida* Infection Model

[0082] Mice are allotted to cages upon their arrival, and allowed to acclimate before being used. Animals are inoculated with a bacterial suspension (*P. multocida* strain 59A006) intraperitoneally. Each experiment has at least 3 non-medicated control groups including one infected with 0.1X challenge dose and two infected with 1X challenge dose; a 10X challenge data group may also be used. Generally, all mice in a given study can be challenged within 30-90 minutes, especially if a repeating syringe (such as a Cornwall® syringe) is used to administer the challenge. Thirty minutes after challenging has begun, the first compound treatment is given. Subcutaneous doses are administered into the loose skin in the back of the neck whereas oral doses are given by means of a feeding needle. In both cases, a volume of 0.2 ml is used per mouse. A control compound of known efficacy administered by the same route is included in each test. Animals are observed daily, and the number of survivors in each group is recorded for 72 hours (three days) post challenge. The PD50 is a calculated dose at which the compound tested protects 50% of a group of mice from mortality due to the bacterial infection which would be lethal in the absence of drug treatment.

Assay V

Murine *Staphylococcus aureus* intraperitoneal infection model

[0083] Mice (female CF-1) are allotted to cages (10 per cage) upon their arrival, and allowed to acclimate for a minimum of 48 hours before being used. Mice are infected intraperitoneally with 0.5 ml of a 3 to 5 x 10^5 colony forming units (CFU)/ml log phase culture of *Staphylococcus aureus* strain UC 6097 in 5% hog gastric mucin. Each experiment has one infected, non-medicated control group. Generally, all mice in a given study can be challenged within 30 to 90 minutes, especially if a repeating syringe (such as a Cornwall® syringe) is used to administer the challenge culture. Thirty minutes after infection has begun, compound treatment is given. It may be necessary for a second person to begin compound dosing if all of the animals have not been challenged at the end of thirty minutes. Subcutaneous doses are administered into the loose skin in the back of the neck whereas oral doses are given by means of a feeding needle. In both cases, a volume of 0.2 ml is used per mouse. A control compound of known efficacy administered by the same route is included in each test. Animals are observed daily, and the number of survivors in each group is recorded for 72 hours (three days) post challenge. The PD50 is a calculated dose at which the compound tested protects 50% of a group of mice from mortality due to the bacterial infection which would be lethal in the absence of drug treatment.

Assay VI

Murine *Staphylococcus aureus* intramammary infection model

[0084] Lactating mice (female CF-1 that gave birth 2 to 5 days prior to the day of infection) (female CF-1) are allotted to cages (1 per cage) upon their arrival, and allowed to acclimate for 24-48 hours before being used. Mice are infected in the L4 mammary gland with 0.1 ml of a 300 to 450 colony forming units (CFU)/ml log phase culture of *Staphylococcus aureus* strain UC 6097. Each experiment has one infected, non-medicated control group. Thirty minutes after infection has begun, compound treatment is given. Subcutaneous doses are administered into the loose skin in the back of the neck whereas oral doses are given by means of a feeding needle. In both cases, a volume of 0.2 ml is used per mouse. The endpoint is the presence or absence of clinical mastitis symptoms and quantitation of bacterial numbers in the mammary glands five days after infection. Bacteria are quantitated by homogenizing the infected gland with 4 volumes of phosphate buffered saline for 30 seconds (Omni International, model TH). The homogenate and dilutions of the homogenate are plated on Brain Heart Infusion Agar, incubated at 37° C overnight, and the colonies counted. The lower limit of detection is 50 CFU/gland. Infected, non-medicated mice have ~ 5 x 10^9 CFU/gland at the time of necropsy.

Assay VII

Determination Of MIC Of *Fusobacterium necrophorum* Isolated Using Anaerobic Plate Dilution Techniques

[0085] Minimum inhibitory concentration (MIC) data may be collected from isolates of *Fusobacterium necrophorum* of cattle and sheep origin. The MIC values for *Fusobacterium necrophorum* are determined using plate dilution techniques and inoculation with a Steer's replicator. The procedures are those outlined in "Methods For Antimicrobial Susceptibility Testing Of Anaerobic Bacteria-Third Edition; Approved Standard" (vol. 13, no. 26, 1993) by the National Committee on Clinical Laboratory Standards (NCCLS). A total of 10 dilutions of the antimicrobials are tested as doubling dilutions of the drug (32 to 0.063 mcg/ml). Control strains of anaerobic bacteria (*Clostridium perfringens* ATCC 13124 and *Bacteroides fragilis* ATCC 25285) are used as controls on each inoculated plate.

[0086] The compounds of the present invention, and the pharmaceutically acceptable salts thereof (hereinafter "the active compounds"), may be administered through oral, parenteral, topical, or rectal routes in the treatment of bacterial and protozoal infections. In general, these compounds are most desirably administered in dosages ranging from about 0.2 mg per kg body weight per day (mg/kg/day) to about 200 mg/kg/day in single or divided doses (i.e., from 1 to 4 doses per day), although variations will necessarily occur depending upon the species, weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 4 mg/kg/day to about 50 mg/kg/day is most desirably employed. Variations may nevertheless occur depending upon the species of mammal, fish or bird being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such larger doses are first divided into several small doses for administration throughout the day.

[0087] In the treatment of cancer, in particular non-small cell lung cancer, the active compounds may be administered

as described in European patent application publication number 758,549, published February 2, 1997.

[0088] The active compounds may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by the routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the active compounds may be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compounds are present in such dosage forms at concentration levels ranging from about 5.0% to about 99% by weight.

[0089] For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral adinistration, the active compound may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

[0090] For parenteral administration, solutions of an active compound in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques will known to those skilled in the art.

[0091] Additionally, it is also possible to administer the active compounds of the present invention topically and this may be done by way of creams, jellies, gels, pastes, patches, ointments and the like, in accordance with standard pharmaceutical practice.

[0092] For administration to animals other than humans, such as cattle or domestic animals, the active compounds may be administered in the feed of the animals or orally as a drench composition.

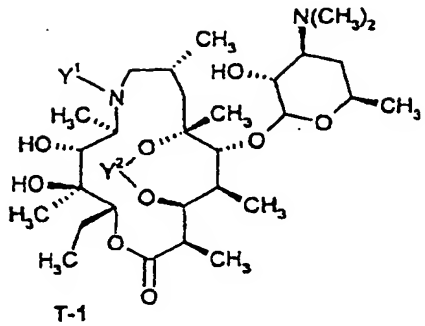
[0093] The active compounds may also be adminstered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

[0094] The active compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide phenyl, polyhydroxyethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoylresidues. Furthermore, the active compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

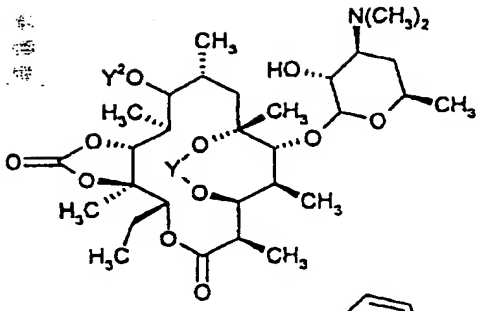
[0095] In Tables 1 and 2 below, "Ex." refers to the Example number; "T" refers to the template structure appearing before the table; "P" refers to the specific method used to prepare the example as described above in Methods A-AP; HPLC I, II, and III refer to the HPLC data associated with the example; and "Mass Spec" refers to the mass spectrometry data associated with the example. The HPLC measurements were conducted using an HP1050 (manufactured by Hewlett Packard) as the instrument with the following detector conditions: 1050 DAD 2nm slit, ELSD tube temp 113°C. HPLC I included the following conditions: column - Prodigy 3.2x250 mm C-8; A=0.050M NH_4OAc + 0.1% TFA freshly prepared, C=acetonitrile; gradient - 80:20 A:C to 20:80 A:C over 30 minutes; flow rate - 0.5 mL/minute. HPLC II included the following conditions: column - YMC 4.6x250 mm C-8; 70% 0.050M NH_4OAc, 30% acetonitrile; flow rate - 1 ml/minute. HPLC III included the following conditions: column - YMC 4.6x250 mm C-8; 65% 0.050M NH_4OAc, 35% acetonitrile; flow rate -1 ml/minute.

Templates For Tables

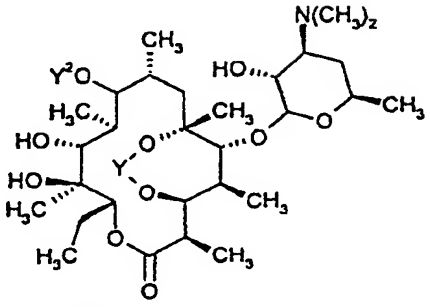
[0096]



T-1

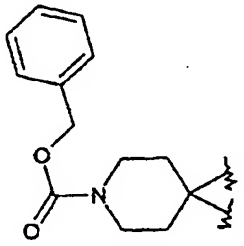


T-2



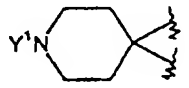
T-3

Y (for T-2 and T-3) =

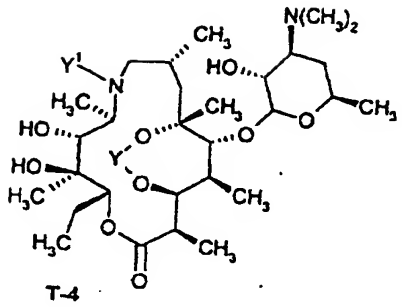


Y(a)

or



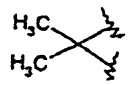
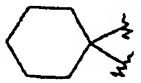
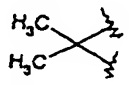
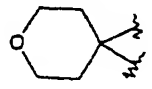
Y(b)

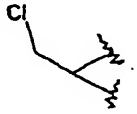
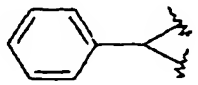
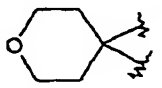
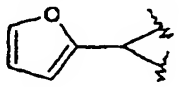
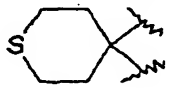
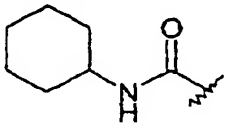


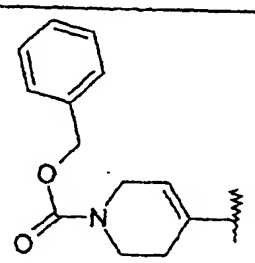
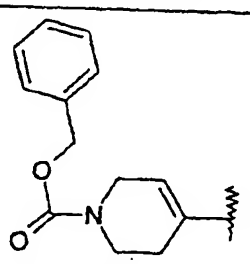
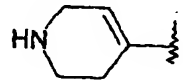
T-4

Y(for T-4)= 

Table 1

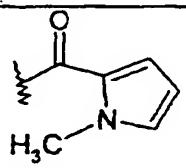
Ex.	T	Y^1	Y^2	P	HPLC I	HPLC II	HPLC III	Mass Spec.
1	T-1	CH_3		A			26.43	632
2	T-1	CH_3		A			75.00	672
3	T-1	H		A			17.92	643
4	T-1	H		A			>60	657
5	T-1	H		A		10.8		617
6	T-1	H		B	10.91			658.7
7	T-4	H	-C(O)O(benzyl)	D		3.28		792.4
8	T-4	H	H	G	4.09	3.13		658.4
9	T-4	CH_3	H	G	3.62	3.74		672.4
10	T-4	CH_3	-C(O)O(benzyl)	D	16.76			806.5

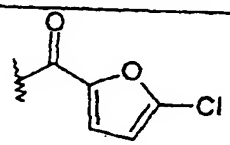
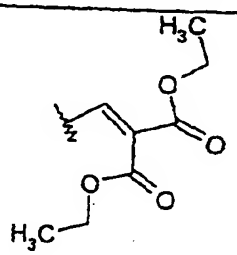
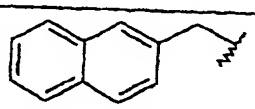
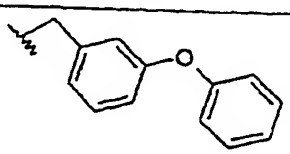
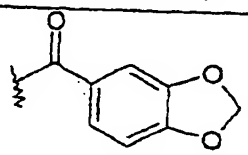
Ex.	T	Y^1	Y^2	P	HPLC I	HPLC II	HPLC III	Mass Spec.
11	T-4	H	$-C(O)CH_3$	F		5.71		700.6
12	T-4	CH_3	CH_3	H		3.71		686.6
13	T-1	H		U				637.4
14	T-1	CH_3		V	18.98			679.6
15	T-1	CH_3		B	9.79			673.4
16	T-4	CH_3	$-C(O)CH_3$	C		10.14		714.5
17	T-1	H		U				655.4
18	T-4	CH_3	$-C(O)OCH_3$	O		35.35		730.5
19	T-4	H	$-C(O)OCH_2CH_3$	C		23.00		730.5
20	T-4	CH_3	$-C(O)OCH_2CH_3$	C	12.93			744.5
21	T-4	CH_3	$-SO_2CH_3$	I		24.14		750.5
22	T-1	H		E	14.38			675.7
23	T-4	CH_3	$-C(O)NHCH(CH_3)_2$	Q		22.21		757.7
24	T-4	CH_3	$-C(O)CH_2OC(O)CH_3$	R		13.87		772.4
25	T-1	CH_3		E	13.83			689.4
26	T-4	CH_3		Q				797.6
27	T-4	H	$-C(O)OC(CH_3)_3$	C	16.47			758.5
28	T-4	CH_3	$-C(O)OC(CH_3)_3$	C	15.54			772.5

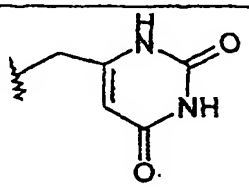
Ex.	T	Y'	Y²	P	HPLC I	HPLC II	HPLC III	Mass Spec.
29	T-2 Y(a)	-	H	B				819
30	T-2 Y(a)	-		B				1034
31	T-3 Y(a)	-	H	B	20.89			793.4
32	T-3 Y(b)	H	H	G		3.80		659.5
33	T-3 Y(b)	CH_3	H	W	7.72			637.4
34	T-4	CH_3	$-C(O)CH_2OH$	T		8.18		730.6
35	T-4	CH_3	-C(O)(cyclopropyl)	S		25.45		740.5
36	T-4	CH_3	$-C(O)CH_2CH_3$	S		16.60		728.4
37	T-2 Y(b)	H		G				900.5
38	T-2 Y(b)	H		G				766.5
39	T-4	CH_3	$-C(O)OCH_2CH=CH_2$	N	14.16			756.4
40	T-4	CH_3	$-C(O)OCH=CH_2$	N	17.15			742 4
41	T-4	CH_3	$-C(O)O(CH_2)_2Cl$	M	13.85			778.3
42	T-4	CH_3	$-C(O)OCH_2C(Cl)_3$	M	21.66			845.6
43	T-4	CH_3	$-C(O)NHCH_2CH=CH_2$	Q		17.92		755.5
44	T-4	CH_3	$-C(O)OCH_2CH(CH_3)_2$	N	19.19			772.5

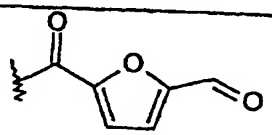
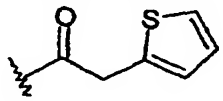
Ex.	T	Y^1	Y^2	P	HPLC I	HPLC II	HPLC III	Mass Spec.
45	T-4	CH_3	$-SO_2(CH_2)_3CH_3$	J	15.39			792.4
46	T-4	CH_3	$-C(O)NHCH_2CH_3$	Q				743.5
47	T-4	CH_3	$-SO_2CH(CH_3)_2$	K	12.83			778.3
48	T-4	CH_3	$-SO_2CH_2CH_3$	K		29.13		764.4
49	T-4	CH_3	benzylsulfonyl	K	15.31			826.4
50	T-4	CH_3	cyclopropyl	U		32.79		712.4
51	T-4		Both Y^1 and Y^2 are cyclopropyl	U				738.4
52	T-4	H	cyclopropyl	U		9.52		698.3
53	T-4	H	$-C(O)OCH_2CH=CH_2$	N		25.38		742.3
54	T-4	H	$-C(O)O(CH_2)_2Cl$	M	13.29			764.2
55	T-4	H	-C(O)(cyclopropyl)	L		10.32		726.5
56	T-4	H	$-C(O)CH_2OH$	L		4.86		716.4
57	T-4	H	$-C(O)CH_2OC(O)CH_3$	L		6.99		758.4
58	T-4	H	$-C(O)OCH_3$	P		12.41		716.4
59	T-4	H	$-C(O)NHCH(CH_3)_2$	Q		9.12		743.5
60	T-4	H	$-SO_2CH_2CH_3$	K		13.57		750.4
61	T-4	CH_3	$-C(O)(CH_2)_2CH_3$	S				742.4
62	T-4	H	$-C(O)CH_2CH_3$	L		8.18		714.5
63	T-4	H	$-C(O)CH_2OCH_3$	L		5.82		730.4
64	T-4	H	$-C(O)H$	L	9.06	5.92		686.4
65	T-4	H	$-C(O)CH_2NH_2$	L	4.92			715.4

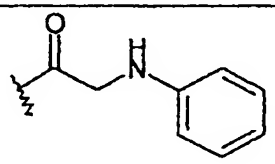
Ex.	T	Y^1	Y^2	P	HPLC I	HPLC II	HPLC III	Mass Spec.
66	T-4	CH_3	$-SO_2CH_2C(O)OCH_3$	K	12.97			808.5
67	T-4	CH_3	$-C(O)CH_2N(CH_3)_2$	AD	6.03			757.5
68	T-4	CH_3	$-C(O)CF_3$	AD				768.4
69	T-4	CH_3	2-furoyl	AD	12.42			766.4
70	T-4	CH_3	$-CH_2C(O)CH_3$	AB	6.43			728.4
72	T-4	CH_3	$-CH_2CH=CH_2$	AE	7.393			712 5
73	T-4	CH_3	4-imidazolylmethylcarbonyl	L	5.00			780.4

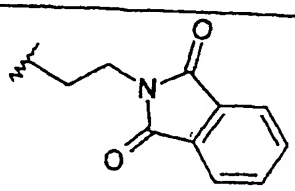
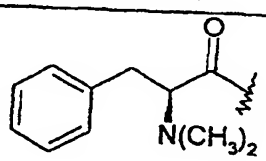
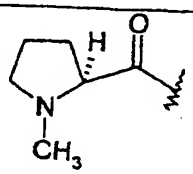
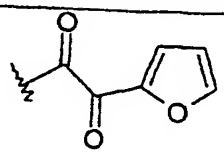
Ex.	T	Y^1	Y^2	P	HPLC I	HPLC II	HPLC III	Mass Spec.
74	T-4	CH_3	$-CH_2C(O)OCH_3$	AB	9.42			744.4
75	T-4	CH_3	2-benzofuranylcarbonyl	AD	16.32			816.1
76	T-4	CH_3	$-C(O)CH_2NHC(O)$(phenyl)	AD	12.66			833.1
77	T-4	CH_3	2-methoxybenzoyl	AD	13.39			806.1
78	T-4	CH_3	2-thienylcarbonyl	AD	13.68			782.3
79	T-4	CH_3		AD	13.46			779.4
80	T-4	CH_3	$-C(O)CH_2NHC(O)CH_3$	AD	7.87			771.4
81	T-4	CH_3	benzyl	AB	10.54			762.6
82	T-4	CH_3	benzoyl	AD	13.65			776.1
83	T-4	CH_3	2-hydroxyethyl	H	4.39			716.4
84	T-4	CH_3	3,5-dimethoxybenzoyl	AD	14.42			836.6
85	T-4	H	2-furoyl	AD	11.75			752.5
86	T-4	H	$-C(O)CH_2N(CH_3)_2$	AD	5.48			743.5
87	T-4	CH_3	$-C(O)CH_2$(1-imidazolyl)	AD	7.31			780.6
88	T-4	CH_3	3-furoyl	AD	12.08			766.5
90	T-4	CH_3	3-furylmethyl	AC	9.06			752.2
91	T-4		Y^1 and Y^2 are both 4-methoxybenzyl	AB				898.8
92	T-4	H	4-methoxybenzyl	AB	10.40			778.6
93	T-4		Y^1 and Y^2 are both 4-chlorobenzyl	AB	23.99			906.6
94	T-4	H	4-chlorobenzyl	AB	12.30			782.5
95	T-4		Y^1 and Y^2 are both 3-methoxybenzyl	AB	16.25			898.7
96	T-4	H	3-methoxybenzyl	AB	10.76			778.6
98	T-4	CH_3	4-methoxybenzyl	AB	10.72			792 5

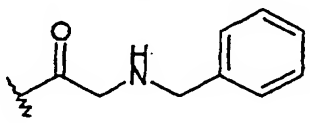
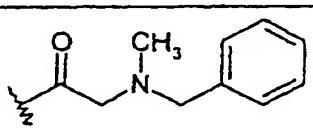
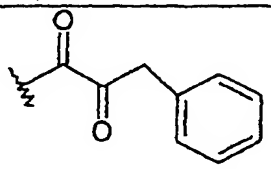
Ex.	T	Y^1	Y^2	P	HPLC I	HPLC II	HPLC III	Mass Spec.
99	T-4	CH_3	4-chlorobenzyl	AB	12.78			796.4
100	T-4	H	benzyl	AB				748.5
101	T-4		Y^1 and Y^2 are both benzyl	AB	14.81			838.5
102	T-4	H	2-pyridylmethyl	AB	7.46			749.5
103	T-4	H	2-quinoxaloyl	AD	13.07			814.5
104	T-4	CH_3	4-biphenylmethyl	AB	15.18			838.5
105	T-4	H		AD	14.09			786.4
106	T-4	H	3,4-dichloro-2-furoyl	AD				820.3
107	T-4	H	3-methyl-2-furoyl	AD	13.27			766.4
108	T-4	H		AO	14.5			828.5
109	T-4	H		AB	13.03			798.5
110	T-4	H		AB	14.97			840.3
111	T-4	H	2-thienylcarbonyl	AD	12.87			768.4
112	T-4	H	2-pyrrolylcarbonyl	AD	11.97			751.5
113	T-4	H	3-methoxybenzoyl	AD	13.48			792.5
114	T-4	H		AD	13.04			806.5

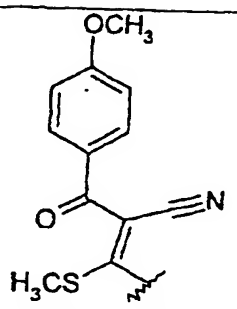
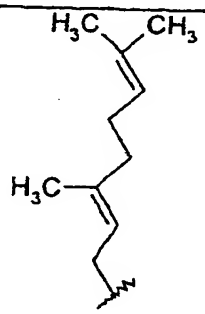
Ex.	T	Y^1	Y^2	P	HPLC I	HPLC II	HPLC III	Mass Spec.
115	T-4	H	4,5-dimethyl-2-furoyl	AD	14.23			780.5
116	T-4	H	4-biphenylcarbonyl	AD				838.6
117	T-4	H	benzyloxycarbonylmethyl	AB	14.84			806.6
118	T-4	H	3-furoyl	AD				752.6
119	T-4	H	benzoyl	AD	12.58			762.5
120	T-4	H	4-bromobenzoyl	AD	15.66			840.5
121	T-4	CH_3	2-hydroxy-3-methoxybenzyl	AC	10.38			808.5
122	T-4	H	4-methoxybenzoyl	AD	13.29			792.5
123	T-4	H	2-chloro-3-pyridylcarbonyl	AD	11.11			797.4
124	T-4	H	2,3-dichloro-5-pyridylcarbonyl	AD	15.25			831.4
125	T-4	H	1-methyl-2-pyrrolylcarbonyl	AD	12.88			765.5
126	T-4	H	2- hydroxy-6-pyridylcarbonyl	AD	8.44			779.5
127	T-4	H	2-pyrazinylcarbonyl	AD	9.44			764.5
128	T-4	H	2-thienylsulfonyl	AD				
129	T-4		Y^1 and Y^2 are both 2-thienylsulfonyl	AD	24.03			949.9
130	T-4	CH_3	4-hydroxy-3-methoxy-benzyl	AC	8.23			808.5
131	T-4	CH_3	4-acetamidobenzyl	AB	7.68			819.6
132	T-4	H		AB	7.25			782.5
133	T-4	H	2-pyridylcarbonyl	AD	9.96			763.4
134	T-4	CH_3	3-chloro-4-hydroxy-5-methoxy benzyl	AC	10.21			842.5
135	T-4	H	2-quinolinylcarbonyl	AD	13.44			813.4
137	T-4	CH_3	2-phenylethylcarbonyl	AD	14.99			804.5

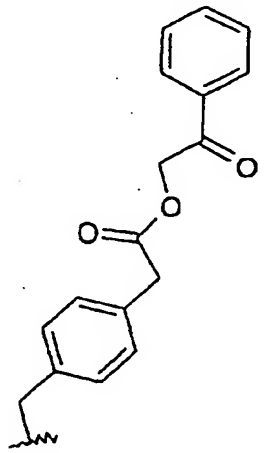
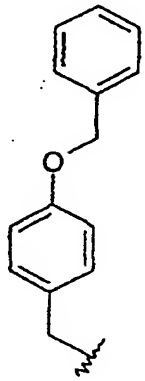
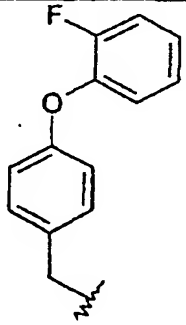
Ex.	T	Y^1	Y^2	P	HPLC I	HPLC II	HPLC III	Mass Spec.
139	T-4	CH_3	2-quinolinylmethyl	AB	11.90			813.7
140	T-4	CH_3	4-quinolinylmethyl	AC	12.82			813.7
141	T-4	CH_3	4-cyanobenzyl	AC				787.8
142	T-4	H		AD	11.37			780.7
143	T-4	CH_3	4-nitrobenzyl	AB	13.09			807.6
144	T-4	CH_3	benzylcarbonyl	AD	14.03			790.5
145	T-4	H	2-quinolinylmethyl	AB	11.45			799.2
146	T-4	H	4-quinolinylmethyl	AC	11.62			799.2
147	T-4	H		AD	13.20			782.6
148	T-4		Y^1 and Y^2 are both 2-quinolinylmethyl	AB	19.03			940.1
149	T-4	CH_3	benzyloxycarbonylmethyl	AB	15.73			820.8
150	T-4	CH_3	2-methoxybenzyl	AB	11.16			792.8
151	T-4	CH_3	3-methoxybenzyl	AB	11.11			792.5
152	T-4	CH_3	2-pyridylmethyl	AB	7.88			763.7
153	T-4	CH_3	3-pyridylmethyl	AB	7.27			763.7

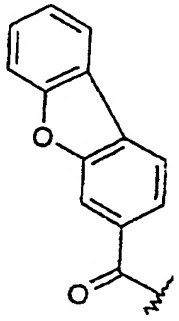
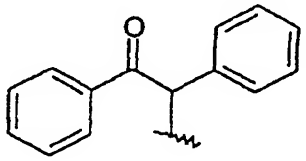
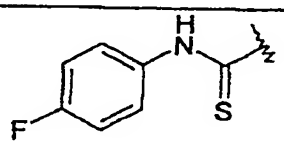
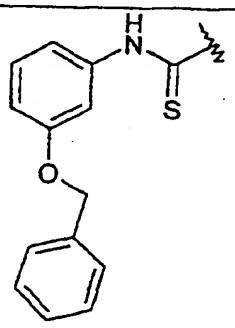
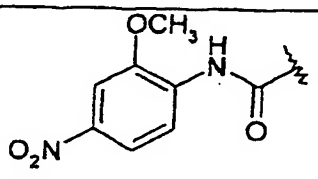
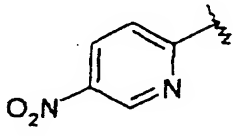
Ex.	T	Y^1	Y^2	P	HPLC I	HPLC II	HPLC III	Mass Spec.
156	T-4	H	2-phenylethylcarbonyl	AD	14.41			790.5
157	T-4	H	benzylcarbonyl	AD	13.64			776.6
158	T-4	CH_3	2-quinoxaloyl	AD	13.68			828.5
159	T-4	CH_3	2-quinolinylcarbonyl	AD	14.07			827.5
160	T-4	CH_3	4-quinolinylcarbonyl	AD	12.33			827.5
161	T-4	H	4-quinolinylcarbonyl	AD	11.81			813.7
162	T-4	CH_3	2-pyridylcarbonyl	AD	10.43			777.6
163	T-4	H	3-pyridylcarbonyl	AD	9.54			763.4
164	T-4	CH_3	3-pyridylcarbonyl	AD	9.93			777.5
165	T-4	H	4-imidazolylcarbonyl	AD				752.6
166	T-4	CH_3	3,4-dichlorobenzyl	AB	15.76			830.4
167	T-4	H	3,4-dichlorobenzyl	AB	14.62			816.5
168	T-4	CH_3	3,5-difluorobenzyl	AB	13.37			798.5
169	T-4	CH_3	4-fluorobenzyl	AB	11.28			780.6
170	T-4	CH_3	4-pyridylmethyl	AB	8.09			763.6
171	T-4	H	4-pyridylcarbonyl	AD	9.51			763.6
172	T-4	CH_3	4-pyridylcarbonyl	AD	9.90			777.6
173	T-4	CH_3	4-trifluoromethylbenzyl	AB	14.78			830.5
174	T-4	H	4-trifluoromethylbenzyl	AB	13.83			816.6
175	T-4	H	$-C(O)C(O)CH_3$	AD	11.19			728.4
176	T-4	CH_3	3-hydroxy-4-methoxybenzyl	AC				808.5
177	T-4	CH_3		AD				805.6
178	T-4	H	5-nitro-2-furoyl	AD	13.82			797.7
179	T-4	H	4-methoxybenzylcarbonyl	AD	13.44			806.6
180	T-4	H	2-hydroxybenzylcarbonyl	AD	12.67			792.4
181	T-4	H	3,5-difluorobenzyl	AB	12.44			784.5
182	T-4	H	2-methoxybenzylcarbonyl	AD	13.92			806.6
183	T-4	H	4-hydroxybenzylcarbonyl	AD	10.73			793.5
184	T-4	H	3-hydroxybenzylcarbonyl	AD	11.24			792.5

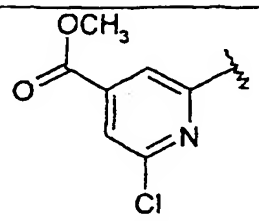
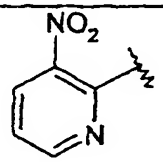
Ex.	T	Y^1	Y^2	P	HPLC I	HPLC II	HPLC III	Mass Spec.
185	T-4	CH_3		AC				854
186	T-4	H	3-methoxyphenoxymethyl-carbonyl	AD				822.8
187	T-4	CH_3	benzoylmethyl	AB	11.70			790.6
188	T-4	CH_3		AD	9.77			847.7
189	T-4	CH_3		AD	6.84			783.6
190	T-4	H	2-indenylcarbonyl	AD	15.43			801.5
191	T-4	H	3-indenylcarbonyl	AD	13.21			801.4
192	T-4	CH_3	2-(bis(2-methoxybenzyl)amino)ethyl	AC				955
193	T-4	H		AD				780.5

194	T-4	CH_3	diphenylphosphinyl	AG	15.80			782.5
195	T-4	CH_3		AD	9.90			819.6
196	T-4	CH_3		AD				833.6
197	T-4	H		AD	15.53			804.5
198	T-4	CH_3	2-phenylethyl	AC	12.24			776.5
199	T-4	CH_3	3-(4-hydroxyphenyl)-2-propenyl	AC	13.11			818.6
200	T-4	H	4-methoxyphenoxymethyl-carbonyl	AD	14.05			822.9
201	T-4	H	2-methoxyphenoxymethyl-carbonyl	AD	13.89			822.9
202	T-4	H	phenoxymethylcarbonyl	AD	14.48			792.5
203	T-4	CH_3	2-(bis(2-phenylethyl)amino)ethyl	AC				923
204	T-4	H	4-methylbenzyl	AB	11.27			762.5
205	T-4	H	2-phenoxyethylcarbonyl	AD	14.87			806.9
206	T-4	H	2-chlorophenoxymethyl-carbonyl	AD				826.4

215	T-4	CH_3		AO	14.85			903.2
216	T-4	CH_3		AB	15.59			808.3

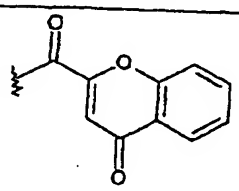
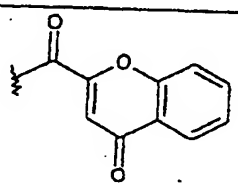
217	T-4	CH_3		AB	14.52			938.5
218	T-4	CH_3		AB	15.36			868.6
219	T-4	CH_3		AB				872.2

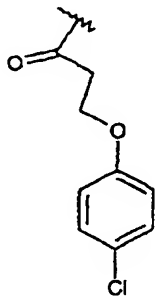
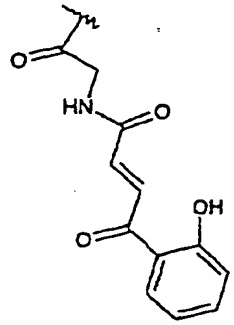
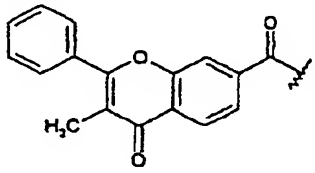
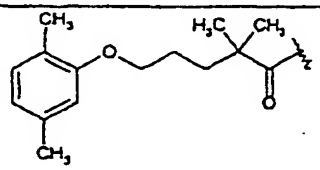
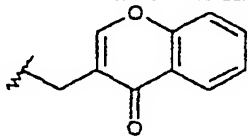
220	T-4	CH_3		L	18.12			866.5
221	T-4	CH_3		AB	16.95			866.6
222	T-4	CH_3		AO	16.59			825.7
223	T-4	CH_3		AO	20.59			913.6
224	T-4	CH_3		AO	17.03			866.3
225	T-4	H		AF	16.14			780.5

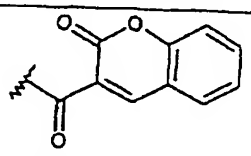
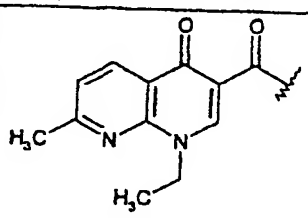
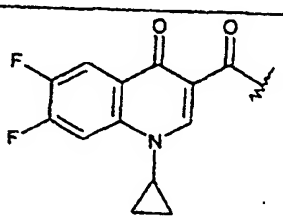
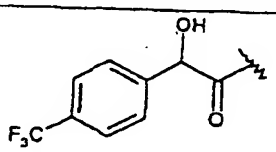
226	T-4	H		AF	19.25			827.5
227	T-4	H		AF	15.96			780.5

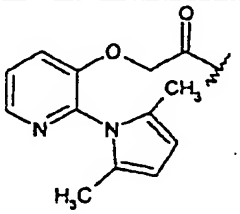
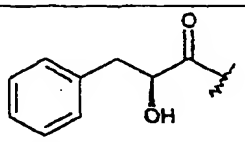
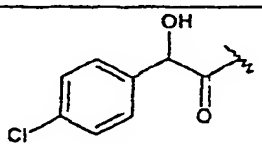
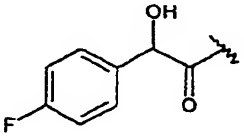
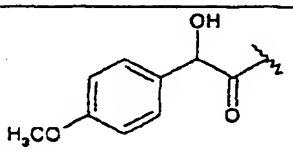
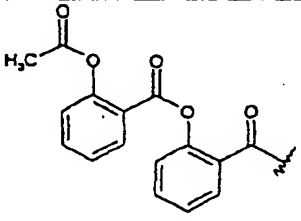
[0097] In Table 2 below, all compounds are based on the T-4 macrolide template illustrated above.

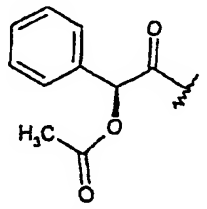
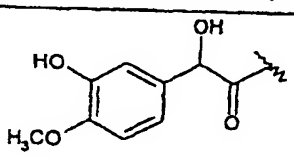
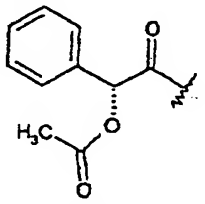
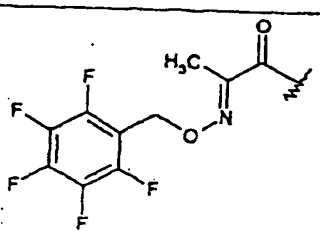
Table 2

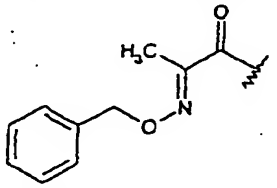
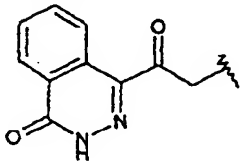
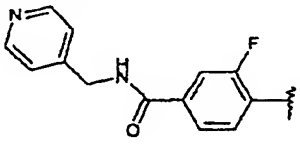
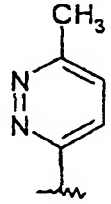
Ex.	Y^1	Y^2	P	Mass Spec.
228	Y^1 is benzyl; Y^2 is 2-pyrazinecarbonyl		AK	854.5
229	Y^1 is 4-methoxybenzyl; Y^2 is 2-pyrazinecarbonyl		AL	884.5
230	CH_3		AD	844.6
231	H		AD	830.8
232	H	7,8-difluoro-3-quinolinecarbonyl	AD	849.6
233	H	3-quinolinecarbonyl	AD	813.8
234	H	3-hydroxy-4-methoxybenzoyl	AD	808.6
235	CH_3	2-pyrazinecarbonyl	AD	778.6

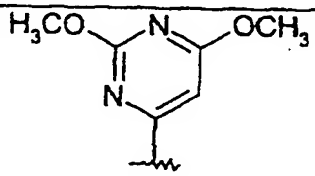
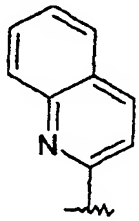
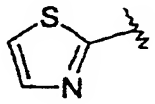
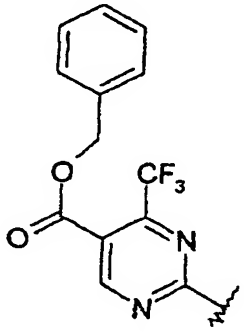
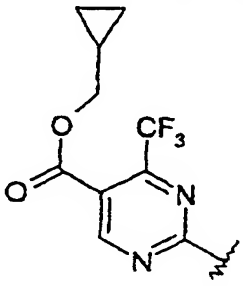
Ex.	Y^1	Y^2	P	Mass Spec.
236	H	3-(4-chlorophenoxy)propionyl	AD	840.7
237	H		AD	808.7
238	H	4-acetamidobenzoyl	AD	819.7
239	H		AD	887.6
240	H		AD	920.6
241	H		AD	890.1
242	H		AC	830.1

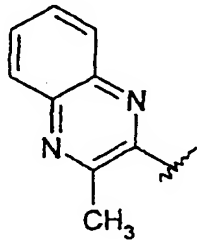
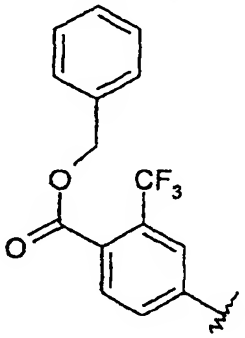
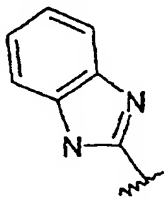
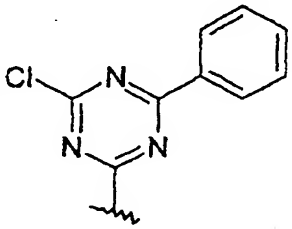
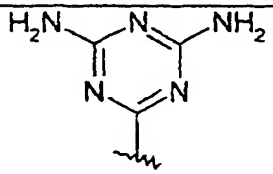
Ex.	Y¹	Y²	P	Mass Spec.
243	H	1-isoquinolinecarbonyl	AD	813.1
244	H	3-isoquinolinecarbonyl	AD	813.1
245	H	4-methoxy-2-quinolinecarbonyl	AD	843.1
246	H		AD	830.2
247	H	4-cinnolinecarbonyl	AD	814.2
248	H		AD	872.2
249	H		AD	905.1
250	H	3,4-dihydroxybenzyl	AC	794.2
251	H	2-hydroxy-3-quinoxalinecarbonyl	AD	830.1
252	H	2-(1-pyrrole)-5-pyridylcarbonyl	AD	828.2
253	H		AD	860.1
254	H	3-benzyloxy-4-methoxybenzoyl	AD	898.6

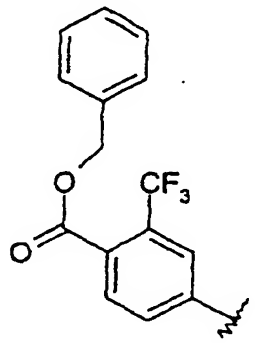
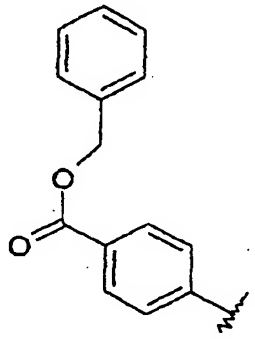
Ex.	Y^1	Y^2	P	Mass Spec.
255	H		AD	886.6
256	CH_3	3-benzyloxy-4-methoxybenzyl	AB	898.6
257	H	3,4-difluorobenzoyl	AD	798.6
258	H	2,4-difluorobenzoyl	AD	798.7
259	H		AD	806.2
260	H	*tert*-butylcarbonyl	AD	742.2
261	H		AD	826.2
262	H		AD	810.1
263	H		AD	822.6
264	H		AD	940.1
265	H	4-methoxy-3-(dimethyl-(*tert*-butyl)silyloxy)benzyl	AB	908.6

Ex.	Y^1	Y^2	P	Mass Spec.
266	H		AD	834.7
267	H	5-benzimidazolecarbonyl	AD	802.6
268	H		AD	838.7
269	H		AD	834.6
270	H	2-benzofurancarbonyl	AD	802.6
271	H	4-acetamidobenzyl	AB	805.6
272	Both Y^1 and Y^2 are 4-acetamidobenzyl		AB	
273	CH_3	2-benzofurancarbonyl	AB	802.6
274	CH_3	3-isobutoxy-4-methoxybenzyl	AB	864.6
275	CH_3	4-methoxy-3-(4-trifluoromethylbenzyloxy)-benzyl	AB	966.6
276	H		AN	923.5

Ex.	Y^1	Y^2	P	Mass Spec.
277	H		AM	833.6
278	CH_3	2-benzimidazolemethyl	AB	802.5
279	H	4-benzyloxycarbonyl-2-fluorophenyl	AH	886.6
280	H	3-hydroxy-4-methoxybenzyl	AC	794.6
281	H	3,6-dichloro-4-pyridazinecarbonyl	AD	832.6
282	H		AD	844.6
283	CH_3		AI	900.5
284	H	4-pyridylcarbonyl	AB	749.1
285	H	3-pyridylcarbonyl	AB	749.1
286	CH_3	3-quinolinecarbonyl	AD	827.1
287	H	3-bis(methylsulfonyl)amino-benzyl	AB	919
288	H	3-ethoxy-4-hydroxybenzyl	AC	808.1
289	H	3-methoxy-4-hydroxybenzyl	AC	794.1
290	CH_3		AQ	764.02

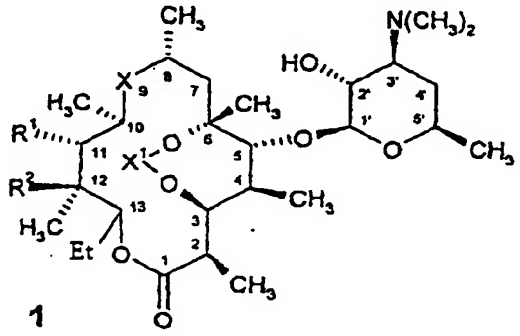
Ex.	Y^1	Y^2	P	Mass Spec.
291	CH_3		AQ	810.05
292	CH_3		AQ	799.06
293	CH_3		AQ	NT
294	CH_3		AQ	952.13
295	CH_3		AQ	916.1

Ex.	Y^1	Y^2	P	Mass Spec.
296	CH_3		AQ	814.09
297	CH_3		AP	950.16
298	CH_3		AQ	788.05
299	CH_3		AQ	861.52
300	CH_3		AQ	781.04

Ex.	Y^1	Y^2	P	Mass Spec.
301	H		AP	936.16
302	CH_3		AP	883.5

Claims

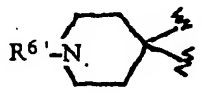
1. A compound of the formula 1



1

or a pharmaceutically acceptable salt or solvate thereof, wherein:

X is $-CH_2NR^6-$ or $-NR^6CH_2-$, wherein the first dash of each of the foregoing X groups is attached to the C-10 carbon of the compound of formula 1 the last dash of each group is attached to the C-8 carbon of the compound of formula 1 and wherein R^6 is H or methyl;
X^1 is

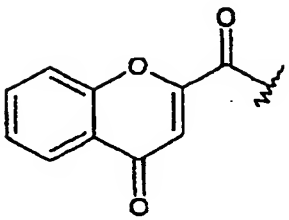


R^1 and R^2 are each OH;
R^3 is independently selected from the group consisting of H, C_1-C_6 alkyl,-$(CH_2)_m$(C_6-C_{10} aryl), and -$(CH_2)_m$(4-10 membered heterocyclic), wherein m is an integer ranging from 0 to 4 and the foregoing R^3 groups are optionally substituted by 1 to 3 R^{13} groups;
$R^{6'}$ is H, hydroxy, formyl, C_1-C_{10} alkoxy, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, $-SO_2$(C_1-C_{10} alkyl), - $(CH_2)_mC(O)CH_2OC(O)$(C_1-C_{10} alkyl), -$(CH_2)_mC(O)(CH_2)$,$NR^{11}R^{12}$, -$(CH_2)_tC(O)$(C_1-C_{10} alkyl), - $(CH_2)_mC(O)(CH_2)_tC(O)$(C_1-C_{10} alkyl), -$(CH_2)_mC(O)(CH_2)_tO$(C_1-C_{10} alkyl), - $(CH_2)_mC(O)(CH_2)_tO$(C_2-C_{10} alkenyl), -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(4-10 membered heterocyclic), - $C(O)(CH_2)_mC(O)(CH_2)_q$(C_6-C_{10} aryl), -$C(O)(CH_2)_mC(O)(CH_2)_q$(4-10 membered heterocyclic), - $(CH_2)_mC(O)(CH_2)_q$(C_6-C_{10} aryl), -$(CH_2)_mC(O)(CH_2)_q$(4-10 membered heterocyclic), - $(CH_2)_qC(O)(CH_2)_mO(CH_2)_t$($C_6$-$C_{10}$ aryl), -$(CH_2)_qC(O)(CH_2)_mO(CH_2)_t$(4-10 membered heterocyclic), -$(CH_2)_tO(CH_2)_m$(C_6-C_{10} aryl), -$(CH_2)_tO(CH_2)_m$(4-10 membered heterocyclic), - $(CH_2)_mC(S)(CH_2)_tNR^{11}R^{12}$, wherein m is an integer ranging from 0 to 4, q and t are each independently an integer ranging from 0 to 5, the heterocyclic moieties of the above $R^{6'}$ groups optionally include an oxo (=O) group on the ring system, and the foregoing $R^{6'}$ groups, except H, formyl and hydroxy, are optionally substituted by 1 to 3 R^{13} groups;
R^{11} and R^{12} are each independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, - $C(O)$(C_1-C_{10} alkyl), -$(CH_2)_m$(C_6-C_{10} aryl),-$C(O)(CH_2)_m$(C_6-C_{10} aryl), -$(CH_2)_m$(4-10 membered heterocyclic), and -$C(O)(CH_2)_m$(4-10 membered heterocyclic), wherein m is an integer ranging from 0 to 4, and the foregoing R^{11} and R^{12} groups, except H, are optionally substituted by 1 to 3 R^{13} groups;
each R^{13} is independently selected from halo, cyano, nitro, trifluoromethyl, azido, - $C(O)R^{16}$, $-C(O)OR^{16}$, $-OC(O)R^{16}$, $-OC(O)OR^{16}$, $-NR^{14}C(O)R^{15}$, $-C(O)NR^{14}R^{15}$, $-NR^{14}R^{15}$, hydroxy, C_1-C_6 alkyl, $-N(SO_2R^{16})_2$, $-NR^{14}SO_2R^{16}$, $-S(O)_j$(C_1-C_6 alkyl) wherein j is an integer ranging from 0 to 2, C_1-C_6 alkoxy, -$(CH_2)_m$(C_6-C_{10} aryl), and -$(CH_2)_m$(4-10 membered heterocyclic), wherein m is an integer ranging from 0 to 4, and the alkyl, alkoxy, aryl and heterocyclic moieties of the above R^{13} substituents are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, $-C(O)R^{16}$, $-C(O)OR^{16}$, $-CO(O)R^{16}$, $-OC(O)OR^{16}$, $-NR^{14}C(O)R^{15}$, $-C(O)NR^{14}R^{15}$, $-NR^{14}R^{15}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;
each R^{14} and R^{15} is independently H, $-OR^7$, C_1-C_6 alkyl, -$(CH_2)_m$(C_6-C_{10} aryl), or -$(CH_2)_m$(4-10 membered heterocyclic), wherein m is an integer ranging from 0 to 4, with the proviso that where R^{14} and R^{15} are both attached to the same nitrogen, then R^{14} and R^{15} are not both $-OR^7$; and
each R^{16} is independently selected from H, C_1-C_{10} alkyl, -$(CH_2)_m$(C_6-C_{10} aryl), and - $(CH_2)_m$(4-10 membered heterocyclic), wherein m is an integer ranging from 0 to 4.

wherein alkyl means saturated monovalent hydrocarbon radicals having straight, cyclic or branched moieties.

2. A compound according to claim $R^{6'}$ wherein is H, hydroxy, hydroxy substituted C_1-C_{10} alkyl, formyl, C_1-C_{10} alkoxy, $-SO_2$(C_1-C_4 alkyl), -$(CH_2)_mC(O)$(C_1-C_{10} alkyl), - $(CH_2)_mC(O)CH_2OC(O)$(C_1-C_{10} alkyl), -$(CH_2)_mC(O)CH_2O$(C_1-C_{10} alkyl), -$(CH_2)_mC(O)(CH_2)_q$(C_6-C_{10} aryl), -$(CH_2)_mC(O)(CH_2)_q$(4-10 membered heterocyclic), -$(CH_2)_t$(4-10 membered heterocyclic), or -$(CH_2)_t$(C_6-C_{10} aryl), wherein m, q and t are each independently 0 or 1.

3. A compound according to claim 1 wherein $R^{6'}$ is selected from: $-C(O)CH_2CH_3$, - $C(O)CH_2OCH_3$, -C(O)H, -C(O)CH_2OH, $-C(O)CH_2OC(O)CH_3$, $-C(O)CH_3$, -4-chlorobenzyl, 2-pyridylmethyl, 4-acetamidobenzyl, 4-hydroxy-3-methoxybenzyl, 3-hydroxy-4-methoxybenzyl, 2-hydroxyethyl, $-C(O)CH_2N(CH_3)_2$, 4-quinolinylmethyl, 2-quinolinylmethyl, $-C(O)CH_2OC(O)CH_3$, - $SO_2CH_2CH_3$, $-SO_2CH(CH_3)_2$, 2-furoyl, benzoyl, 1-methyl-2-pyrrolylcarbonyl, 2-pyrazinylcarbonyl, 2-pyridylcarbonyl, 2-quinolinylcarbonyl, 3-pyridylcarbonyl, 3-cinnolinecarbonyl, 3-quinolinylcarbonyl, 4-benzyloxycarbonyl-2-fluorophenyl, and



4. A pharmaceutical composition for the treatment of a bacterial, parasitic or protozoal infection, or a disorder related to a bacterial, parasitic or protozoal infection, in a mammal, fish, or bird which comprises a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

5. The pharmaceutical composition of claim 4 wherein said infection or disorder is pneumonia, otitis media, sinusitus, bronchitis, tonsillitis, or mastoiditis related to infection by *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus,* or *Peptostreptococcus* spp.; pharynigitis, rheumatic fever, or glomerulonephritis related to infection by *Streptococcus pyogenes,* Groups C and G streptococci, *Clostridium diptheriae,* or *Actinobacillus haemolyticum;* a respiratory tract infections related to infection by *Mycoplasma pneumoniae, Legionella pneumophila, Streptococcus pneumoniae, Haemophilus influenzae,* or *Chlamydia pneumoniae;* uncomplicated skin or soft tissue infection, abscess or osteomyelitis, or puerperal fever related to infection by *Staphylococcus aureus,* coagulase-positive staphylococci (i.e., *S. epidermidis, S. hemolyticus,* etc.), *Streptococcus pyogenes, Streptococcus agalactiae,* Streptococcal groups C-F (minute-colony streptococci), viridans streptococci, *Corynebacterium minutissimum, Clostridium* spp., or *Bartonella henselae;* uncomplicated acute urinary tract infection related to infection by *Staphylococcus saprophyticus* or *Enterococcus* spp.; urethritis, or cervicitis; a sexually transmitted disease related to infection by *Chlamydia trachomatis, Haemophilus ducreyi, Treponema pallidum, Ureaplasma urealyticum,* or *Neiserria gonorrheae;* toxin disease related to infection by *S. aureus* (food poisoning or toxic shock syndrome), or Groups A, B, and C streptococci; ulcer related to infection by *Helicobacter pylori;* systemic febrile syndrome related to infection by *Borrelia recurrentis;* Lyme disease related to infection by *Borrelia burgdorferi;* conjunctivitis, keratitis, and dacrocystitis related to infection by *Chlamydia trachomatis, Neisseria gonorrhoeae, S. aureus, S. pneumoniae, S. pyogenes, H. influenzae,* or *Listeria* spp.; disseminated *Mycobacterium avium* complex (MAC) disease related to infection by *Mycobacterium avium,* or *Mycobacterium intracellulare;* gastroenteritis related to infection by *Campylobacter jejuni;* intestinal protozoa related to infection by *Cryptosporidium* spp.; odontogenic infection related to infection by viridans streptococci; persistent cough related to infection by *Bordetella pertussis;* gas gangrene related to infection by *Clostridium perfringens* or *Bacteroides* spp.; atherosclerosis or cardiovascular disease related to infection by *Helicobacter pylori* or *Chlamydia pneumoniae;* bovine respiratory disease related to infection by *P. haemolytica, P. multocida, Mycoplasma bovis,* or *Bordetella* spp.; cow enteric disease related to infection by *E. coli* or protozoa; dairy cow mastitis related to infection by *Staph. aureus, Strep. uberis, Strep. agalactiae, Strep. dysgalactiae, Klebsiella* spp., *Corynebacterium,* or *Enterococcus* spp.; swine respiratory disease related to infection by *A. pleuro., P. multocida,* or *Mycoplasma* spp.; swine enteric disease related to infection by *E. coli, Lawsonia intracellularis, Salmonella,* or *Serpulina hyodysinteriae;* cow footrot related to infection by *Fusobacterium* spp.; cow metritis related to infection by *E. coli;* cow hairy warts related to infection by *Fusobacterium necrophorum* or *Bacteroides nodosus;* cow pink-eye related to infection by *Moraxella bovis;* cow premature abortion related to infection by protozoa; urinary tract infection in a dog or cat related to infection by *E. coli;* skin or soft tissue infection in a dog or cat related to infection by *Staph. epidermidis, Staph. intermedius, coagulase neg. Staph.* or *P. multocida;* or dental or mouth infection in a dog or cat related to infection by *Alcaligenes* spp., *Bacteroides* spp., *Clostridium* spp., *Enterobacterspp., Eubacterium, Peptostreptococcus, Porphyromonas,* or *Prevotella.*

6. Used of a compound according to claim 1 for the manufacture of a medicament for treating a bacterial, parasitic or protozoal infection, or a disorder related to a bacterial, parasitic or protozoal infection, in a mammal, fish, or bird,

7. Use as claimed in claim 6 wherein said infection or disorder is
pneumonia, otitis media, sinusitus, bronchitis, tonsillitis, or mastoiditis related to infection by *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus,* or *Peptostreptococcus* spp.; pharynigitis, rheumatic fever, or glomerulonephritis related to infection by *Streptococcus pyogenes,* Groups C and G streptococci, *Clostridium diptheriae,* or *Actinobacillus haemolyticum;* a respiratory tract infections related to

infection by *Mycoplasma pneumoniae, Legionella pneumophila, Streptococcus pneumoniae, Haemophilus influenzae,* or *Chlamydia pneumoniae;* uncomplicated skin or soft tissue infection, abscess or osteomyelitis, or puerperal fever related to infection by *Staphylococcus aureus,* coagulase-positive staphylococci (i.e., *S. epidermidis, S. hemolyticus,* etc.), *Streptococcus pyogenes, Streptococcus agalactiae,* Streptococcal groups C-F (minute-colony streptococci), viridans streptococci, *Corynebacterium minutissimum, Clostridium* spp., or *Bartonella henselae;* uncomplicated acute urinary tract infection related to infection by *Staphylococcus saprophyticus* or *Enterococcus* spp.; urethritis, or cervicitis; a sexually transmitted disease related to infection by *Chlamydia trachomatis, Haemophilus ducreyi, Treponema pallidum, Ureaplasma urealyticum,* or *Neiserria gonorrheae;* toxin disease related to infection by *S. aureus* (food poisoning or toxic shock syndrome), or Groups A, B, and C streptococci; ulcer related to infection by *Helicobacter pylori;* systemic febrile syndrome related to infection by *Borrelia recurrentis;* Lyme disease related to infection by *Borrelia burgdorferi;* conjunctivitis, keratitis, and dacrocystitis related to infection by *Chlamydia trachomatis, Neisseria gonorrhoeae, S. aureus, S. pneumoniae, S. pyogenes, H. influenzae,* or *Listeria* spp.; disseminated *Mycobacterium avium* complex (MAC) disease related to infection by *Mycobacterium avium,* or *Mycobacterium intracellulare;* gastroenteritis related to infection by *Campylobacter jejuni;* intestinal protozoa related to infection by *Cryptosporidium* spp.; odontogenic infection related to infection by viridans streptococci; persistent cough related to infection by *Bordetella pertussis;* gas gangrene related to infection by *Clostridium perfringens* or *Bacteroides* spp.; atherosclerosis or cardiovascular disease related to infection by *Helicobacter pylori* or *Chlamydia pneumoniae;* bovine respiratory disease related to infection by *P. haemolytica, P. multocida, Mycoplasma bovis,* or *Bordetella* spp.; cow enteric disease related to infection by *E. coli* or protozoa; dairy cow mastitis related to infection by *Staph. aureus, Strep uberis, Strep. agalactiae, Strep. dysgalactiae, Klebsiella* spp., *Corynebacterium,* or *Enterococcus* spp.; swine respiratory disease related to infection by *A. pleuro., P. multocida,* or *Mycoplasma* spp.; swine enteric disease related to infection by *E. coli, Lawsonia intracellularis, Salmonella,* or *Serpulina hyodysinteriae;* cow footrot related to infection by *Fusobacterium* spp.; cow metritis related to infection by *E. coli;* cow hairy warts related to infection by *Fusobacterium necrophorum* or *Bacteroides nodosus;* cow pinkeye related to infection by *Moraxella bovis;* cow premature abortion related to infection by protozoa; urinary tract infection in a dog or cat related to infection by *E. coli;* skin or soft tissue in a dog or cat related to infection by *Staph epidermidis, Staph. intermedius, coagulase neg. Staph* or *P. multocida;* or dental or mouth infection in a dog or cat related to infection by *Alcaligenes* spp., *Bacteroides* spp., *Clostridium* spp., *Enterabacter* spp., *Eubacterium, Peptostreptococcus, Porphyromones,* or *Prevotella.*

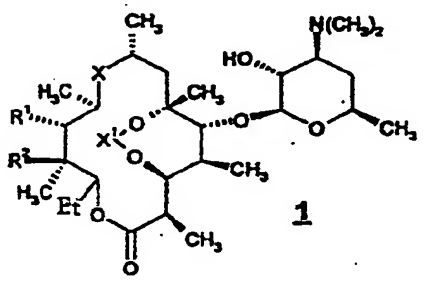
8. A pharmaceutically composition for the treatement of cancer in a mammal which comprises a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

9. A pharmaceutically composition of claim 8 wherein said cancer is non-small cell lug cancer.

10. Use of a compound according to claim 1 for the manufacture of medicament for treating cancer in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of claim 1 .

11. Use as claimed in claim 12 wherein said cancer is non-small cell lug cancer.

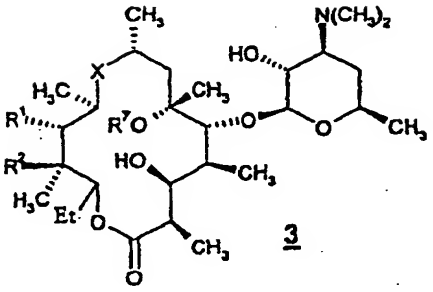
12. A method of preparing a compound of the formula 1



1

as defined in claim 1

which comprises treating a compound of the formula



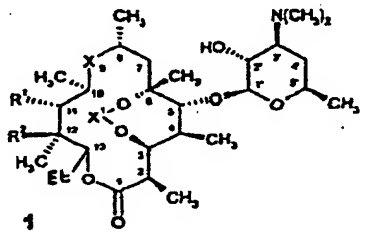
3

with a compound of the formula

in an aprotic solvent in the presence of pyridinium p-toluenesulfonate or p-toluenesulfonic acid monohydrate, or both pyridinium p-toluenesulfonate and p-toluenesulfonic acid monohydrate.

Patentansprüche

1. Verbindung der Formel 1

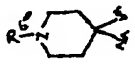


1

oder ein pharmazeutisch verträgliches Salz oder Solvat davon, worin:

X $-CH_2NR^6-$ oder $-NR^6CH_2-$ darstellt, wobei der erste Strich von jeder der vorangehenden Gruppen X an das C-10-Kohlenstoffatom der Verbindung der Formel 1 gebunden ist und der letzte Strich von jeder Gruppe an das C-8-Kohlenstoffatom der Verbindung der Formel 1 gebunden ist, und wobei R^6 H oder Methyl darstellt,

X^1



darstellt,

R^1 und R^2 jeweils OH darstellen;

R^3 unabhängig ausgewählt ist aus der Gruppe, bestehend aus H, C_1-C_6-Alkyl, $-(CH_2)_m(C_6$-C_{10}-Aryl) und $-(CH_2)_m$(4-10-gliedrigem Heterocyclus), worin m eine ganze Zahl im Bereich von 0 bis 4 ist und die vorangehenden Gruppen R^3 gegebenenfalls mit 1 bis 3 Gruppen R^{13} substituiert sind;

$R^{6'}$ H, Hydroxy, Formyl, C_1-C_{10}-Alkoxy, C_1-C_{10}-Alkyl, C_2-C_{10}-Alkenyl, $-SO_2(C_1$-C_{10}-Alkyl), $-(CH_2)_mC$ (O)

$CH_2OC(O)$ (C_1-C_{10}-Alkyl), -$(CH_2)_mC(O)$ $(CH_2)_tNR^{11}R^{12}$, -$(CH_2)_tC(O)$ (C_1-C_{10}-Alkyl), - $(CH_2)_mC(O)$ $(CH_2)_tC(O)$ (C_1-C_{10}-Alkyl), -$(CH_2)_mC(O)$ $(CH_2)_tO(C_1$-$C_{10})$-Alkyl), -$(CH_2)_mC(O)$ $(CH_2)_tO(C_2$-C_{10}-Alkenyl) , - $(CH_2)_t$ (C_6-C_{10}-Aryl), - $(CH_2)_t$(4-10-gliedrigen Heterocyclus), -C(O) $(CH_2)_mC(O)$ $(CH_2)_q$ (C_6-C_{10}-Aryl), -C(O) $(CH_2)_mC(O)$ $(CH_2)_q$(4-10-gliedrigen Heterocyclus), -$(CH_2)_mC(O)$ $(CH_2)_q$ (C_6-C_{10}-Aryl), - $(CH_2)_mC(O)$ $(CH_2)_q$ (4-10-gliedrigen Heterocyclus), - $(CH_2)_qC(O)$ $(CH_2)_mO$ $(CH_2)_t$ (C_6-C_{10}-Aryl), - $(CH_2)_qC(O)$ $(CH_2)_mO(CH_2)_t$ (4-10-gliedrigen Heterocyclus), - $(CH_2)_tO(CH_2)_m$ (C_6-C_{10}-Aryl), - $(CH_2)_tO(CH_2)_m$(4-10-gliedrigen Heterocyclus), -$(CH_2)_mP(O)R^3R^{16}$, - SO_2 $(CH_2)_t$ (C_6-C_{10}-Aryl) oder -$SO_2(CH_2)_t$ (4-10-gliedrigen Heterocyclus), - $(CH_2)_mC(S)$ $(CH_2)_t$ NR^{11} R^{12} darstellt, worin m eine ganze Zahl im Bereich von 0 bis 4 ist, q und t jeweils unabhängig eine ganze Zahl im Bereich von 0 bis 5 sind, die heterocyclischen Einheiten der vorstehend genannten Gruppen $R^{6'}$ gegebenenfalls eine Gruppe Oxo(=0) am Ringsystem einschließen, und die vorangehenden Gruppen $R^{6'}$, mit Ausnahme von H, Formyl und Hydroxy, gegebenenfalls mit 1 bis 3 Gruppen R^{13} substituiert sind;

R^{11} und R^{12} jeweils unabhängig ausgewählt sind aus H, C_1-C_{10}-Alkyl, C_2-C_{10}-Alkenyl, -C(O) (C_1-C_{10}-Alkyl), -$(CH_2)_m$(C_6-C_{10}-Aryl), -C(O) $(CH_2)_m$(C_6-C_{10}-Aryl), -$(CH_2)_m$(4-10-gliedrigem Heterocyclus) und -C(O) $(CH_2)_m$ (4-10-gliedrigem Heterocyclus), worin m eine ganze Zahl im Bereich von 0 bis 4 ist, und die vorangehenden Gruppen R^{11} und R^{12}, mit Ausnahme von H, gegebenenfalls mit 1 bis 3 Gruppen R^{13} substituiert sind;

jedes R^{13} unabhängig ausgewählt ist aus Halogen, Cyano, Nitro, Trifluormethyl, Azido, -C(O)R^{16}, -C(O)OR^{16}, -OC(O)R^{16}, -OC(O)OR^{16}, -$NR^{14}C(O)R^{15}$, -C(O)$NR^{14}R^{15}$, -$NR^{14}R^{15}$, Hydroxy, C_1-C_6-Alkyl, -$N(SO_2R^{16})_2$, -$NR^{14}SO_2R^{16}$, -$S(O)_j$(C_1-C_6-Alkyl), worin j eine ganze Zahl im Bereich von 0 bis 2 ist, C_1-C_6-Alkoxy, -$(CH_2)_m$ (C_6-C_{10}-Aryl) und -$(CH_2)_m$(4-10-gliedrigen Heterocyclus), worin m eine ganze Zahl im Bereich von 0 bis 4 ist und die Alkyl-, Alkoxy-, Aryl- und heterocyclischen Einheiten der vorangehenden Substituenten R^{13} gegebenenfalls mit 1 bis 3 Substituenten, unabhängig ausgewählt aus Halogen, Cyano, Nitro, Trifluoromethyl, Azido, -C(O)R^{16}, -C(O)OR^{16}, - CO (O) R^{16}, -OC (O) OR^{16}, -$NR^{14}C(O)$ R^{15}, -C (O) $NR^{14}R^{15}$, -$NR^{14}R^{15}$, Hydroxy, C_1-C_6-Alkyl und C_1-C_6-Alkoxy, substituiert sind;

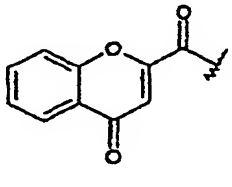
jedes R^{14} und R^{15} unabhängig H, -OR^7, C_1-C_6-Alkyl, - $(CH_2)_m$(C_6-C_{10}-Aryl) oder -$(CH_2)_m$(4-10-gliedrigen Heterocyclus) darstellt, worin m eine ganze Zahl im Bereich von 0 bis 4 ist, mit der Maßgabe, dass, wenn R^{14} und R^{15} beide an das gleiche Stickstoffatom gebunden sind, dann R^{14} und R^{15} nicht beide -OR^7 sind; und

jedes R^{16} unabhängig ausgewählt ist aus H, C_1-C_{10}-Alkyl, $(CH_2)_m$(C_6-C_{10}-Aryl) und -$(CH_2)_m$(4-10-gliedrigem Heterocyclus), worin m eine ganze Zahl im Bereich von 0 bis 4 ist;

worin Alkyl gesättigte, einwertige Kohlenwasserstoffreste mit geraden, cyclischen oder verzweigten Einheiten bedeutet.

2. Verbindung nach Anspruch 1, worin $R^{6'}$ H, Hydroxy, Hydroxy-substituiertes C_1-C_{10}-Alkyl, Formyl, C_1-C_{10}-Alkoxy, -SO_2(C_1-C_4-Alkyl), -$(CH_2)_mC(O)$ (C_1-C_{10}-Alkyl), - $(CH_2)_mC(O)CH_2OC(O)$ (C_1-C_{10}-Alkyl), -$(CH_2)_mC(O)CH_2O$ (C_1-C_{10}-Alkyl), - $(CH_2)_mC(O)$ $(CH_2)_q$(C_6-C_{10}-Aryl), -$(CH_2)_mC(O)$ $(CH_2)_q$(4-10-gliedrigen Heterocyclus), -$(CH_2)_t$ (4-10-gliedrigen Heterocyclus) oder -$(CH_2)_t$(C_6-C_{10}-Aryl) darstellt, worin m, q und t jeweils unabhängig 0 oder 1 sind.

3. Verbindung nach Anspruch 1, worin $R^{6'}$ ausgewählt ist aus: -$C(O)CH_2CH_3$, -$C(O)CH_2OCH_3$, -C(O)H, -C (O) CH_2OH, -$C(O)CH_2OC(O)CH_3$, -$C(O)CH_3$, -4-Chlorbenzyl, 2-Pyridylmethyl, 4-Acetamidobenzyl, 4-Hydroxy-3-methoxybenzyl, 3-Hydroxy-4-methoxybenzyl, 2-Hydroxyethyl, -C (O) CH_2N $(CH_3)_2$, 4-Chinolinylmethyl, 2-Chinolinylmethyl, -$C(O)CH_2OC(O)CH_3$, - $SO_2CH_2CH_3$, -$SO_2CH(CH_3)_2$, 2-Furoyl, Benzoyl, 1-Methyl-2-pyrrolylcarbonyl, 2-Pyrazinylcarbonyl, 2-Pyridylcarbonyl, 2-Chinolinylcarbonyl, 3-Pyridylcarbonyl, 3-Cinnolincarbonyl, 3-Chinolinylcarbonyl, 4-Benzyloxycarbonyl-2-fluorphenyl und



4. Pharmazeutische Zusammensetzung zur Behandlung einer bakteriellen, parasitären oder Protozoeninfektion oder einer Störung, die durch eine bakterielle, parasitäre oder Protozoeninfektion bedingt ist, bei einem Säuger, Fisch oder Vogel, welche eine therapeutisch wirksame Menge einer Verbindung nach Anspruch 1 und einen pharma-

zeutisch verträglichen Träger umfasst.

5. Pharmazeutische Zusammensetzung nach Anspruch 4, wobei die Infektion oder Störung bedeutet Pneumonia, Otitis media, Sinusitus, Bronchitis, Tonsillitis oder Mastoiditis, die durch Infektion durch *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus oder Peptostreptococcus spp.* bedingt sind; Pharynigitis, rheumatisches Fieber oder Glomerulonephritis, die durch Infektion durch *Streptococcus pyogenes*, Gruppen C und G streptococci, *Clostridium diphtheriae oder Actinobacillus haemolyticum* bedingt sind; Atmungstraktinfektionen, die durch Infektion durch *Mycoplasma pneumoniae, Legionella pneumophila, Streptococcus pneumoniae, Haemophilus influenzae oder Chlamydia pneumoniae* bedingt sind; unkomplizierte Haut- oder Weichgewebsinfektionen, Abszess oder Osteomyelitis oder Kindbettfieber, die durch Infektion durch *Staphylococcus aureus,* Koagulase-positive Staphylococci (d.h. *S. epidermidis, S. hemolyticus, usw.), Streptococcus pyogenes, Streptococcus agalactiae,* Streptococcalgruppen C-F (Kurzkolonie Streptococci), Viridans Streptococci, *Corynebacterium minutissimum, Clostridium spp.* oder *Bartonella henselae* bedingt sind; unkomplizierte akute Harntraktinfektion, die durch Infektion durch *Staphylococcus saprophyticus* oder *Enterococcus spp.* bedingt ist; Urethritis oder Cervicitis; eine sexuell übertragene Erkrankung, die durch Infektion durch *Chlamydia trachomatis, Haemophilus ducreyi, Treponema pallidum, Ureaplasma urealyticum* oder *Neisseria gonorrheae* bedingt ist; Toxinerkrankung, die durch Infektion durch *S.* aureus (Lebensmittelvergiftung oder toxisches Schocksyndrom), oder Gruppen A, B und C-Streptococci bedingt ist; Geschwür, das durch Infektion durch *Helicobacter pylori* bedingt ist; systemisches Fiebersyndrom, das durch Infektion durch *Borrelia recurrentis* bedingt ist; Lyme-Krankheit, die durch Infektion durch *Borrelia burgdorferi* bedingt ist; Konjunktivitis, Keratitis und Dacrocystitis, die durch Infektion durch *Chlamydia trachomatis, Neisseria gonorrhoeae, S. aureus, S. pneumoniae, S. pyogenes, H. influenzae* oder *Listeria spp.* bedingt sind; disseminierte *Mycobacterium* avium-Komplex (MAC)-Krankheit, die durch Infektion durch *Mycobacterium avium* oder *Mycobacterium intracellulare* bedingt ist; Gastroenteritis, die durch Infektion durch *Campylobacter jejuni* bedingt ist; Intestinalprotozoa, die durch Infektion durch *Cryptosporidium* spp. bedingt sind; odontogene Infektion, die durch Infektion durch Viridans-Streptococci bedingt ist; persistenter Husten, der durch Infektion durch *Bordetella pertussis* bedingt ist; Gasgangrän, das durch Infektion durch *Clostridium perfringens* oder *Bacteroides spp.* bedingt ist; Atherosklerose oder cardiovasculäre Krankheit, die durch Infektion durch *Helicobacter pylori* oder *Chlamydia pneumoniae* bedingt ist; Erkrankung des Atmungstrakts beim Rind, die durch Infektion durch *P. haemolytica, P. multocida, Mycoplasma bovis* oder *Bordetella spp.* bedingt ist; enterische Erkrankung beim Rind, die durch Infektion durch *E. coli* oder Protozoa bedingt ist; Milchkuhmastitis, die durch Infektion durch *Staph. aureus, Strep. uberis, Strep. agalactiae, Strep. dysgalactiae, Klebsiella spp., Corynebacterium* oder *Enterococcus spp.* bedingt ist; Erkrankung des Atmungstrakts beim Schwein, die durch Infektion durch *A. pleuro., P. multocida* oder *Mycoplasma spp.* bedingt ist; enterische Erkrankung beim Schwein, die durch Infektion durch *E. coli, Lawsonia intracellularis, Salmonella* oder *Serpulina hyodysinteriae* bedingt ist; Rinderklauenfäule, die durch Infektion durch *Fusobacterium spp.* bedingt ist; Rindermetritis, die durch Infektion durch *E. coli* bedingt ist; Rinderhaarwarzen (cow hairy warts), die durch Infektion durch *Fusobacterium necrophorum* oder *Bacteroides nodosus* bedingt sind; Konjunktivitis beim Rind, die durch Infektion durch *Moraxella bovis* bedingt ist; Verkalben, das durch Infektion durch Protozoa bedingt ist; Harntraktinfektion bei einem Hund oder einer Katze, die durch Infektion durch *E. coli* bedingt ist; Haut- oder Weichgewebsinfektion bei einem Hund oder einer Katze, die durch Infektion durch *Staph. epidermidis, Staph. intermedius, Coagulase neg. Staph.* oder *P. multocida* bedingt ist; oder dentale oder Mundinfektion bei einem Hund oder einer Katze, die durch Infektion durch *Alcaligenes spp., Bacteroides spp., Clostridium spp., Enterobacter spp., Eubacterium, Peptostreptococcus, Porphyromonas* oder *Prevotella* bedingt ist.

6. Verwendung einer Verbindung nach Anspruch 1 zur Herstellung eines Arzneimittels zum Behandeln einer bakteriellen, parasitären oder Protozoeninfektion, oder einer durch eine bakterielle, parasitäre oder Protozoeninfektion bedingten Störung bei einem Säuger, Fisch oder Vogel.

7. Verwendung nach Anspruch 6, wobei die Infektion oder Störung bedeutet Pneumonia, Otitis media, Sinusitis, Bronchitis, Tonsillitis oder Mastoiditis, die durch Infektion durch *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus oder Peptostreptococcus spp.* bedingt sind; Pharynigitis, rheumatisches Fieber oder Glomerulonephritis, die durch Infektion durch *Streptococcus pyogenes*, Gruppen C und G streptococci, Clostridium *diphtheriae oder Actinobacillus haemolyticum* bedingt sind; Atmungstraktinfektionen, die durch Infektion durch *Mycoplasma pneumoniae, Legionella pneumophila, Streptococcus pneumoniae, Haemophilus influenzae oder Chlamydia pneumoniae* bedingt sind; unkomplizierte Haut- oder Weichgewebsinfektionen, Abszess oder Osteomyelitis oder Kindbettfieber, die durch Infektion durch *Staphylococcus aureus,* Koagulase-positive Staphylococci (d.h. *S. epidermidis, S. hemolyticus, usw.), Streptococcus pyogenes, Streptococcus agalactiae,* Streptococcalgruppen C-F (Kurzkolonie Streptococci), Viridans

Streptococci, *Corynebacterium minutissimum, Clostridium spp.* oder *Bartonella henselae* bedingt sind; unkomplizierte akute Harntraktinfektion, die durch Infektion durch *Staphylococcus saprophyticus* oder *Enterococcus spp.* bedingt ist; Urethritis oder Cervicitis; eine sexuell übertragene Erkrankung, die durch Infektion durch *Chlamydia trachomatis, Haemophilus ducreyi, Treponema pallidum, Ureaplasma urealyticum* oder *Neisseria gonorrheae* bedingt ist; Toxinerkrankung, die durch Infektion durch *S. aureus* (Lebensmittelvergiftung oder toxisches Schocksyndrom), oder Gruppen A, B und C-Streptococci bedingt ist; Geschwür, das durch Infektion durch *Helicobacter pylori* bedingt ist; systemisches Fiebersyndrom, das durch Infektion durch *Borrelia recurrentis* bedingt ist; Lyme-Krankheit, die durch Infektion durch *Borrelia burgdorferi* bedingt ist; Konjunktivitis, Keratitis und Dacrocystitis, die durch Infektion durch *Chlamydia trachomatis, Neisseria gonorrhoeae, S. aureus, S. pneumoniae, S. pyogenes, H. influenzae* oder *Listeria spp.* bedingt sind; disseminierte *Mycobacterium* avium-Komplex (MAC)-Krankheit, die durch Infektion durch *Mycobacterium avium* oder *Mycobacterium intracellulare* bedingt ist; Gastroenteritis, die durch Infektion durch *Campylobacter jejuni* bedingt ist; Intestinalprotozoa, die durch Infektion durch *Cryptosporidium spp.* bedingt sind; odontogene Infektion, die durch Infektion durch Viridans-Streptococci bedingt ist; persistenter Husten, der durch Infektion durch *Bordetella pertussis* bedingt ist; Gasgangrän, das durch Infektion durch *Clostridium perfringens* oder *Bacteroides spp.* bedingt ist; Atherosklerose oder cardiovasculäre Krankheit, die durch Infektion durch *Helicobacter pylori* oder *Chlamydia pneumoniae* bedingt ist; Erkrankung des Atmungstrakts beim Rind, die durch Infektion durch *P. haemolytica, P. multocida, Mycoplasma bovis* oder *Bordetella spp.* bedingt ist; enterische Erkrankung beim Rind, die durch Infektion durch *E. coli* oder Protozoa bedingt ist; Milchkuhmastitis, die durch Infektion durch *Staph. aureus, Strep. uberis, Strep. agalactiae, Strep. dysgalactiae, Klebsiella spp., Corynebacterium* oder *Enterococcus spp.* bedingt ist; Erkrankung des Atmungstrakts beim Schwein, die durch Infektion durch *A. pleuro., P. multocida* oder *Mycoplasma spp.* bedingt ist; enterische Erkrankung beim Schwein, die durch Infektion durch *E. coli, Lawsonia intracellularis, Salmonella* oder *Serpulina hyodysinteriae* bedingt ist; Rinderklauenfäule, die durch Infektion durch *Fusobacterium spp.* bedingt ist; Rindermetritis, die durch Infektion durch *E. coli* bedingt ist; Rinderhaarwarzen (cow hairy warts), die durch Infektion durch *Fusobacterium necrophorum* oder *Bacteroides nodosus* bedingt sind; Konjunktivitis beim Rind, die durch Infektion durch *Moraxella bovis* bedingt ist; Verkalben, das durch Infektion durch Protozoa bedingt ist; Harntraktinfektion bei einem Hund oder einer Katze, die durch Infektion durch *E. coli* bedingt ist; Haut- oder Weichgewebsinfektion bei einem Hund oder einer Katze, die durch Infektion durch *Staph. epidermidis, Staph. intermedius, Coagulase neg. Staph.* oder *P. multocida* bedingt ist; oder dentale oder Mundinfektion bei einem Hund oder einer Katze, die durch Infektion durch *Alcaligenes spp., Bacteroides spp., Clostridium spp., Enterobacter spp., Eubacterium, Peptostreptococcus, Porphyromonas* oder *Prevotella* bedingt ist.

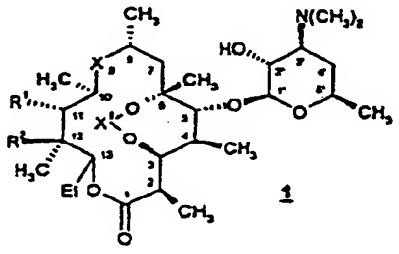
8. Pharmazeutische Zusammensetzung zur Behandlung von Krebs bei einem Säuger, die eine therapeutisch wirksame Menge einer Verbindung nach Anspruch 1 und einen pharmazeutisch verträglichen Träger umfasst.

9. Pharmazeutische Zusammensetzung nach Anspruch 8, wobei der Krebs ein nicht-kleinzelliger Lungenkrebs ist.

10. Verwendung einer Verbindung nach Anspruch 1 zur Herstellung eines Arzneimittels für die Behandlung von Krebs bei einem Säuger, die Verabreichen einer therapeutisch wirksamen Menge einer Verbindung nach Anspruch 1 an den Säuger umfasst.

11. Verwendung nach Anspruch 10, wobei der Krebs nicht-kleinzelliger Lungenkrebs ist.

12. Verfahren zum Herstellen einer Verbindung der Formel 1,



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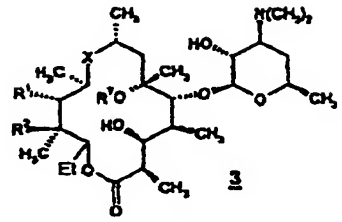
wie in Anspruch 1 definiert,

das Behandeln einer Verbindung der Formel



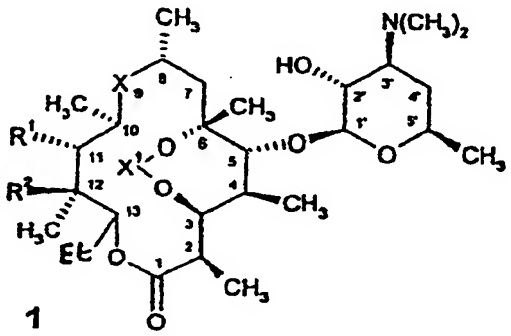
3

mit einer Verbindung der Formel

in einem aprotischen Lösungsmittel in Gegenwart von Pyridinium-p-toluolsulfonat oder p-Toluolsulfonsäuremonohydrat oder sowohl Pyridinium-p-toluolsulfonat als auch p-Toluolsulfonsäuremonohydrat umfasst.

Revendications

1. Composé de formule 1



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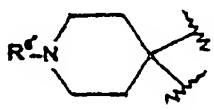
ou un de ses sels ou produits de solvatation pharmaceutiquement acceptables, formule dans laquelle :

X représente un groupe $-CH_2NR^6-$ ou $-NR^6CH_2-$, dans lequel le premier tiret de chacun des groupes X précités est fixé à l'atome de carbone C-10 du composé de formule 1 et le dernier tiret de chaque groupe est fixé à l'atome de carbone C-8 du composé de formule 1, et dans lequel R^6 représente H ou un groupe méthyle;

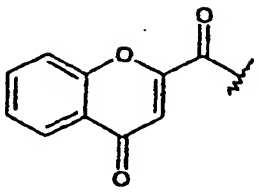
X^1 représente un groupe



R^1 et R^2 représentent chacun un groupe OH ;
R^3 est choisi indépendamment dans le groupe consistant en H, des groupes alkyle en C_1 à C_6, - $(CH_2)_m$(aryle en C_6 à C_{10}) et -$(CH_2)_m$(hétérocyclique tétra- à décagonal), dans lesquels m représente un nombre entier de 0 à 4 et les groupes R^3 précités sont facultativement substitués avec 1 à 3 groupes R^{13} ;
$R^{6'}$ représente H, un groupe hydroxy, formyle, alkoxy en C_1 à C_{10}, alkyle en C_1 à C_{10}, alcényle en C_2 à C_{10}, - SO_2 (alkyle en C_1 à C_{10}), - $(CH_2)_mC(O)CH_2OC(O)$ (alkyle en C_1 à C_{10}), - $(CH_2)_m$ $(C(O)$ $(CH_2)_tNR^{11}R^{12}$, - $(CH_2)_tC(O)$ (alkyle en C_1 à C_{10}), - $(CH_2)_mC(O)$ $(CH_2)_tC(O)$ (alkyle en C_1 à C_{10}), - $(CH_2)_mC(O)$ $(CH_2)_tO$ (alkyle en C_1 à C_{10}), - $(CH_2)_mC$ (O) $(CH_2)_tO$ (alcényle en C_2 à C_{10}), - $(CH_2)_t$ (aryle en C_6 à C_{10}), - $(CH_2)_t$ (hétérocyclique tétra- à décagonal), -C(O) $(CH_2)_mC(O)$ $(CH_2)_q$(aryle en C_6 à C_{10}), -$C(O)(CH_2)_mC$ (O) $(CH_2)_q$(hétérocyclique tétra- à décagonal) , - $(CH_2)_m$ C(O) $(CH_2)_q$(aryle en C_6 à C_{10}), - $(CH_2)_mC(O)$ $(CH_2)_q$(hétérocyclique tétra- à décagonal) , -$(CH_2)_qC(O)(CH_2)_mO(CH_2)_t$(aryle en C_6 à C_{10}) , - $(CH_2)_qC$ (O) $(CH_2)_mO$ $(CH_2)_t$ (hétérocyclique tétra- à décagonal) , - $(CH_2)_tO(CH_2)_m$(aryle en C_6 à C_{10}), - $(CH_2)_tO(CH_2)_m$(hétérocyclique tétra-à décagonal), - $(CH_2)_mP(O)R^3R^{16}$, -SO_2 $(CH_2)_t$ (aryle en C_6 à C_{10}), ou -SO_2 $(CH_2)_t$(hétérocyclique tétra- à décagonal) , - $(CH_2)_mC(S)$ $(CH_2)_tNR^{11}R^{12}$, dans lequel m représente un nombre entier de 0 à 4, q et t représentent chacun indépendamment un nombre entier de 0 à 5, les groupements hétérocycliques des groupes $R^{6'}$ précités comprennent facultativement un groupe oxo (=O) sur le système cyclique et les groupes $R^{6'}$ précités, à l'exception de H, formyle et hydroxyle, sont facultativement substitués avec 1 à 3 groupes R^{13} ;
R^{11} et R^{12} sont choisis chacun indépendamment entre H, des groupes alkyle en C_1 à C_{10}, alcényle en C_2 à C_{10}, - C (O) (alkyle en C_1 à C_{10}), - $(CH_2)_m$ (aryle en C_6 à C_{10}), - C (O) $(CH_2)_m$ (aryle en C_6 à C_{10}) , - $(CH_2)_m$ (hétérocyclique tétra-à décagonal) et -C(O) $(CH_2)_m$(hétérocyclique tétra- à décagonal), dans lesquels m représente un nombre entier de 0 à 4, et les groupes R^{11} et R^{12} précités, à l'exception de H, sont facultativement substitués avec 1 à 3 groupes R^{13};
chaque groupe R^{13} est choisi indépendamment entre des groupes halogéno, cyano, nitro, trifluorométhyle, azido, -C(O)R^{16}, - C(O)OR^{16}, -OC (O) R^{16}, -OC (O) OR^{16}, -NR^{14}C(O)R^{15}, -C(O)N$R^{14}R^{15}$, -N$R^{14}R^{15}$, hydroxy, alkyle en C_1 à C_6, -$N(SO_2R^{16})_2$, -N$R^{14}SO_2R^{16}$, -S $(O)_j$ (alkyle en C_1 à C_6) dans lequel j représente un nombre entier de 0 à 2, alkoxy en C_1 à C_6, -$(CH_2)_m$(aryle en C_6 à C_{10}) et -$(CH_2)_m$(hétérocyclique tétra- à décagonal), dans lesquels m représente un nombre entier de 0 à 4, et les groupements alkyle, alkoxy, aryle et hétérocyclique des substituants R^{13} précités sont facultativement substitués avec 1 à 3 substituants choisis indépendamment entre des substituants halogéno, cyano, nitro, trifluorométhyle, azido, -C(O)R^{16}, - C(O)OR^{16}, -CO (O)R^{16}, -OC(O)OR^{16}, -NR^{14}C(O)R^{15}, -C(O)N$R^{14}R^{15}$, -N$R^{14}R^{15}$, hydroxy, alkyle en C_1 à C_6 et alkoxy en C_1 à C_6 ;
chacun des groupes R^{14} et R^{15} représente indépendamment H, un groupe -OR^7, alkyle en C_1 à C_6, - $(CH_2)_m$ (aryle en C_6 à C_{10}) ou - $(CH_2)_m$(hétérocyclique tétra- à décagonal), dans lesquels m représente un nombre entier de 0 à 4, sous réserve que, lorsque R^{14} et R^{15} sont l'un et l'autre fixés au même atome d'azote, alors R^{14} et R^{15} ne représentent pas l'un et l'autre un groupe -OR^7 ; et
chaque groupe R^{16} est choisi indépendamment entre H, des groupes alkyle en C_1 à C_{10}, -$(CH_2)_m$(aryle en C_6 à C_{10}), et - $(CH_2)_m$(hétérocyclique tétra- à décagonal) dans lesquels m représente un nombre entier de 0 à 4 ; le terme alkyle désignant des radicaux hydrocarbonés monovalents saturés comprenant des groupements droits, cycliques ou ramifiés.

2. Composé suivant la revendication 1, dans lequel $R^{6'}$ représente H, un groupe hydroxy, alkyle en C_1 à C_{10} à substituant hydroxy, formyle, alkoxy en C_1 à C_{10}, -SO_2 (alkyle en C_1 à C_4) , - $(CH_2)_mC$ (O) (alkyle en C_1 à C_{10}) , - $(CH_2)_mC$ (O) CH_2OC (O) (alkyle en C_1 à C_{10}) , - $(CH_2)_mC(O)CH_2O$ (alkyle en C_1 à C_{10}), - $(CH_2)_mC$ (O) $(CH_2)_q$ (aryle en C_6 à C_{10}) , - $(CH_2)_mC(O)$ $(CH_2)_q$ (hétérocyclique tétra- à décagonal) , - $(CH_2)_t$(hétérocyclique tétra- à décagonal) ou -$(CH_2)_t$(aryle en C_6 à C_{10}) , dans lequel m, q et t sont chacun égaux indépendamment à 0 ou 1.

3. Composé suivant la revendication 1, dans lequel $R^{6'}$ est choisi entre des groupes : -$C(O)CH_2CH_3$, -$C(O)CH_2OCH_3$, -C(O)H, - $C(O)CH_2OH$, -C (O) CH_2OC (O) CH_3, -C (O) CH_3, -4-chlorobenzyl, 2-pyridylméthyle, 4-acétamidobenzyle, 4-hydroxy-3-méthoxybenzyle, 3-hydroxy-4-méthoxybenzyle, 2-hydroxyéthyle, -C (O) CH_2N $(CH_3)_2$, 4-quinolinylméthyle, 2-quinolinylméthyle, -$C(O)CH_2OC(O)CH_3$, - $SO_2CH_2CH_3$, -$SO_2CH(CH_3)_2$, 2-furoyl, benzoyl, 1-méthyl-2-pyrrolylcarbonyle, 2-pyrazinylcarbonyle, 2-pyridylcarbonyle, 2-quinolinylcarbonyle, 3-pyridylcarbonyle, 3-cinnolinecarbonyle, 3-quinolinylcarbonyle, 4-benzyloxycarbonyl-2-fluorophényle, et



4. Composition pharmaceutique pour le traitement d'une infection par des bactéries, des parasites ou des protozoaires, ou d'un trouble en rapport avec une infection par des bactéries, des parasites ou des protozoaires, chez un mammifère, un poisson ou un oiseau, qui comprend une quantité thérapeutiquement efficace d'un composé suivant la revendication 1 et un support pharmaceutiquement acceptable.

5. Composition pharmaceutique suivant la revendication 4, dans laquelle ladite infection ou ledit trouble est la pneumonie, l'otite moyenne, la sinusite, la bronchite, l'amygdalite ou la mastoïdite en rapport avec une infection par *Streptococcus pneumoniae, Haemophilus* influenzae, *Moraxella catarrhalis, Staphylococcus aureus* ou *Peptostreptococcus* spp. ; la pharyngite, la fièvre rhumatismale ou la glomérulonéphrite en rapport avec une infection par *Streptococcus pyogenes,* les streptocoques des Groupes C et G, *Clostridium diptheriae* ou *Actinobacillus haemolyticum ;* une infection du tractus respiratoire due à *Mycoplasma pneumoniae, Legionella pneumophila, Streptococcus pneumoniae, Haemophilus influenzae* ou *Chlamydia pneumoniae* ; une infection de la peau ou d'un tissu mou, un abcès ou l'ostéomyélite, sans complication, ou la fièvre puerpérale dues à une infection par *Staphylococcus aureus,* de staphylocoques coagulase-positifs (c'est-à-dire *S. epidermidis, S. hemolyticus,* etc.), Streptococcus *pyogenes, Streptococcus agalactiae,* les streptocoques des Groupes C et F (streptocoques en colonies minuscules), les streptocoques du type viridans, *Corynebacterium minutissimum, Clostridium* spp. ou *Bartonella henselae* ; une infection aiguë du tractus urinaire, sans complications, due à un *Staphylococcus saprophyticus* ou *Enterococcus* spp. ; l'urétrite ou la cervicite ; une maladie sexuellement transmissible due à une infection par *Chlamydia trachomatis, Haemophilis ducreyi, Treponema pallidum, Ureaplasma urealyticum* ou *Neisseria gonorrheae ;* une maladie provoquée par une toxine due à une infection par *S. aureus* (empoisonnement alimentaire ou syndrome de choc toxique), ou les streptocoques des Groupes A, B et C ; un ulcère du à une infection par *Helicobacter pylori* ; le syndrome fébrile généralisé dû à une infection par *Borrelia recurrentis ;* la maladie de Lyme due à une infection par *Borrelia burgdorferi* ; la conjonctivite, la kératite et la dacrocystite dues à une infection par *Chlamydia trachomatis, Neisseria gonorrhoeae, S. aureus, S. pneumoniae, S. pyogenes, H. influenzae ou Listeria* spp. ; la maladie du syndrome à *Mycobacterium avium* disséminé (MAC) due à une infection par *Mycobacterium avium* ou *Mycobacterium intracellulare ;* la gastroentérite due à une infection par *Campylobacter jejuni* ; une infection par des protozoaires intestinaux *Cryptosporidium* spp. ; une infection odontogène due à des streptocoques du type viridans ; la toux persistante due à une infection par *Bordetella pertussis ;* la gangrène gazeuse due à une infection par *Clostridium perfringens* ou *Bacteroides* spp. ; l'athérosclérose ou une maladie cardiovasculaire due à une infection par *Helicobacter pylori* ou *Chlamydia pneumoniae ;* une maladie respiratoire bovine due à une infection par *P. haemolytica, P. multocida, Mycoplasma bovis* ou *Bordetella* spp. ; la maladie entérique de la vache due à une infection par *E. coli* ou des protozoaires ; la mastite des vaches laitières due à une infection par *Staph. aureus, Strep. uberis, Strep. agalactiae, Strep. dysgalactiae, Klebsiella* spp., *Corynebacterium* ou *Enterococcus* spp. ; la maladie respiratoire porcine due à une infection par *A. pleuro, P. multocida* ou *Mycoplasma* spp. ; la maladie entérique porcine due à une infection par *E. coli, Lawsonia intracellularis, Salmonella* ou *Serpulina hyodysenteriae ;* le plétin de la vache dû à une infection par *Fusobacterium* spp. ; la métrite de la vache due à une infection par *E. coli ;* les verrues villeuses de la vache dues à une infection par *Fusobacterium necrophorum* ou *Bacteroides nodosus ;* la conjonctivite de la vache due à une infection par *Moraxella bovis* ; l'avortement prématuré des vaches dû à une infection par des protozoaires ; une infection du tractus urinaire chez un chien ou un chat due à *E. coli ;* une infection de la peau ou d'un tissu mou chez un chien ou un chat due à *Staph. epidermis, Staph. intermedius,* un *Staph.* coagulase-nég. ou *P. multocida* ; une infection dentaire ou buccale chez un chien ou un chat due à *Alcaligenes* spp. ; *Bacteroides* spp., *Clostridium* spp., *Enterobacter* spp., *Eubacterium, Peptostreptococcus, Porphyromonas* ou *Prevotella.*

6. Utilisation d'un composé suivant la revendication 1 pour la production d'un médicament destiné au traitement d'une infection par des bactéries, des parasites ou des protozoaires, ou d'un trouble, en rapport avec une infection par des bactéries, des parasites ou des protozoaires chez un mammifère un poisson ou un oiseau.

7. Utilisation suivant la revendication 6, dans laquelle ladite infection ou ledit trouble est la pneumonie, l'otite moyenne,

la sinusite, la bronchite, l'amygdalite ou la mastoïdite en rapport avec une infection par *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus,* ou *Peptostreptococcus* spp ; la pharyngite, la fièvre rhumatismale ou la glomérulonéphrite en rapport avec une infection par *Streptococcus pyogenes,* les streptocoques des Groupes C et G, *Clostridium diptheriae* ou *Actinobacillus haeolyticum ;* une infection du tractus respiratoire due à la *Mycoplasma pneumoniae, Legionella pneumophila, Streptoccus pneumoniae, Haemophilus influenza* ou *Chlamydia pneumoniae ;* une infection de la peau ou d'un tissu mou, un abcès ou l'ostéomyélite, sans complications, ou la fièvre puerpérale dus à une infection par *Staphylococcus aureus,* de staphylocoques coagulase-positifs (c'est-à-dire *S. epidermidis, S. hemolyticus,* etc.), *Streptococcus pyogenes, Streptoccus* agalactiae, les streptocoques des Groupes C et F (streptocoques en colonies minuscules), les streptocoques du type viridans, *Corynebacterium minutissimum, Clostridium* spp. ou *Bartonella henselae* ; une infection aiguë du tractus urinaire, sans complications, due à un *Staphylococcus saprophyticus* ou *Enterococcus* spp. ; l'uréthrite ou la cervicite ; une maladie sexuellement transmissible due à une infection par *Chlamydia trachomatis, Haemophilis ducreyi, Treponema pallidum, Ureaplasma urealyticum* ou *Neisseria gonorrheae* ; une maladie provoquée par une toxine due à une infection par *S. aureus* (empoisonnement alimentaire ou syndrome de choc toxique), ou les streptocoques des Groupes A, B et C ; un ulcère dû à une infection par *Helicobacter pylori* ; le syndrome fébrile généralisé dû à une infection par *Borrelia recurrentis ;* la maladie de Lyme due à une infection par *Borrelia burgdorferi* ; la conjonctivite, la kératite et la dacrocystite dues à une infection par *Chlamydia trachomatis, Neisseria gonorrhoeae, S. aureus, S. pneumoniae, S. pyogenes, H. influenzae ou Listeria* spp. ; la maladie du syndrome à *Mycobacterium avium* disséminé (MAC) due à une infection par *Mycobacterium avium* ou *Mycobacterium intracellulare* ; la gastroentérite due à une infection par *Campylobacter jejuni* ; une infection par des protozoaires intestinaux *Cryptosporidium* spp. ; une infection odontogène due à des streptocoques du type viridans ; la toux persistante due à une infection par *Bordetella pertussis ;* la gangrène gazeuse due à une infection par *Clostridium perfringens* ou *Bacteroides* spp. ; l'athérosclérose ou une maladie cardiovasculaire due à une infection par *Helicobacter pylori* ou *Chlamydia pneumoniae* ; une maladie respiratoire bovine due à une infection par *P. haemolytica, P. multocida, Mycoplasma bovis* ou *Bordetella* spp. ; la maladie entérique de la vache due à une infection par *E. coli* ou des protozoaires ; la mastite des vaches laitières due à une infection par *Staph. aureus, Strep. uberis, Strep. agalactiae, Strep. dysgalactiae, Klebsiella* spp., *Corynebacterium* ou *Enterococcus* spp. ; la maladie respiratoire porcine due à une infection par *A. pleuro, P. multocida* ou *Mycoplasma* spp. ; la maladie entérique porcine due à une infection par *E. coli, Lawsonia intracellularis, Salmonella* ou *Serpulina hyodysenteriae ;* le piétin de la vache dû à une infection par *Fusobacterium* spp. ; la métrite de la vache due à une infection par *E. coli ;* les verrues villeuses de la vache dues à une infection par *Fusobacterium necrophorum* ou *Bacteroides nodosus ;* la conjonctivite de la vache due à une infection par *Moraxella bovis* ; l'avortement prématuré des vaches dû à une infection par des protozoaires ; une infection du tractus urinaire chez un chien ou un chat due à *E. coli* ; une infection de la peau ou d'un tissu mou chez un chien ou un chat due à *Staph. epidermis, Staph. intermedius,* un *Staph.* coagulase-nég. ou *P. multocida* ; une infection dentaire ou buccale chez un chien ou un chat due à *Alcaligenes* spp. ; *Bacteroides* spp., *Clostridium* spp., *Enterobacter* spp., *Eubacterium, Peptostreptococcus, Porphyromonas* ou *Prevotella.*

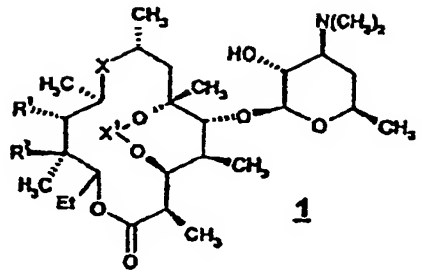
8. Composition pharmaceutique pour le traitement du cancer chez un mammifère, qui comprend une quantité thérapeutiquement efficace d'un composé suivant la revendication 1 et un support pharmaceutiquement acceptable.

9. Composition pharmaceutique suivant la revendication 8, dans lequel ledit cancer est le cancer pulmonaire non à petites cellules.

10. Utilisation d'un composé suivant la revendication 1 pour la production d'un médicament destiné au traitement du cancer chez un mammifère, qui comprend l'administration audit mammifère d'une quantité thérapeutiquement efficace d'un composé suivant la revendication 1.

11. Utilisation suivant la revendication 12, dans laquelle ledit cancer est le cancer pulmonaire non à petites cellules.

12. Procédé pour la préparation d'un composé de formule 1



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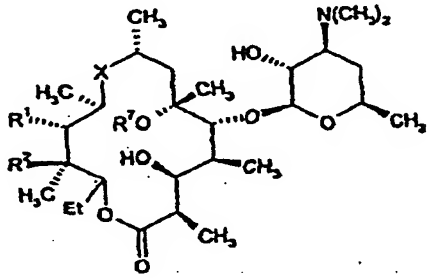
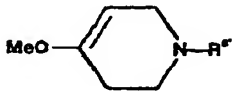
répondant à la définition figurant dans la revendication 1
qui comprend le traitement d'un composé de formule



avec un composé de formule



dans un solvant aprotique en présence de p-toluènesulfonate de pyridinium ou de monohydrate d'acide p-toluènesulfonique, ou bien à la fois de p-toluènesulfonate de pyridinium et de monohydrate d'acide p-toluènesulfonique.